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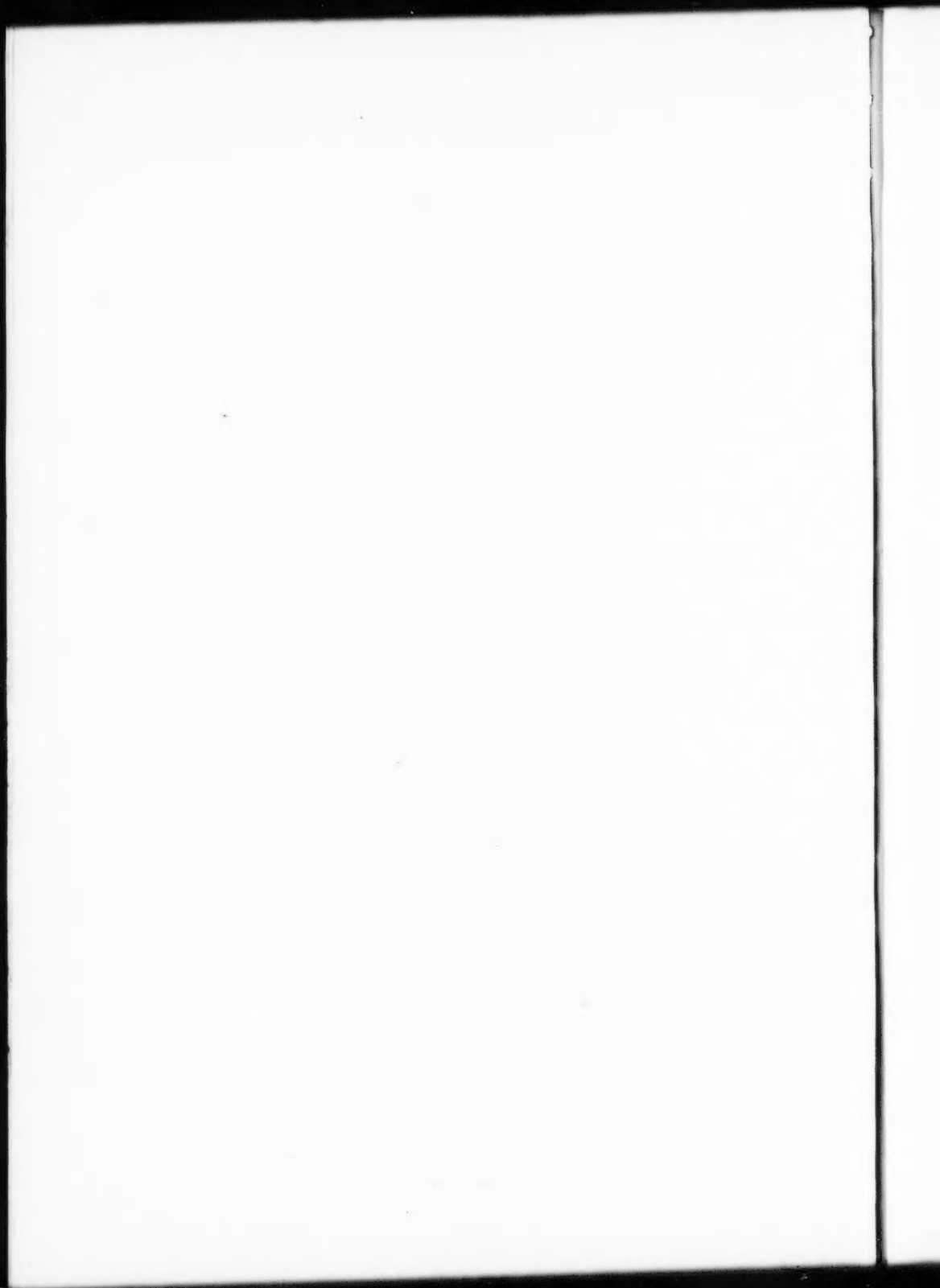
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THE
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APRIL 1, 1914

NO. I

THE CIRCULATION OF THE BLOOD IN MAN AT
HIGH ALTITUDES

I. THE PULSE RATE, ARTERIAL, CAPILLARY, AND VENOUS
PRESSURES

BY EDWARD C. SCHNEIDER AND DWIGHT L. SISCO

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WE purpose in a series of papers to consider circulation data obtained in Colorado Springs, altitude 6000 feet, and on Pike's Peak, altitude 14,109 feet, dealing first with the influence of low barometric pressure upon men living a comparatively inactive life muscularly and second with the influence when moderate muscular activity, and sometimes strenuous exercise such as hard mountain climbing, is added. For the prosecution of such a study Pike's Peak offers unusual advantages. It is essential that the physiological conditions, apart from the reduced atmospheric pressure, should be normal as far as possible. A cog-wheel railway ascends to the very summit of the Peak, affording easy transport for men and apparatus, which permits the elimination of muscular fatigue due to climbing. Further advantages are a substantial stone building well heated and an excellent table provided with the same variety of foods available in Colorado Springs.

In this paper appears a part of the data obtained in Colorado Springs during a period of one and a half years and in three expeditions to the summit of Pike's Peak. The first sojourn on the Peak by Havens and Schneider was for three days, October 12, 13, and 14, 1912; the second, upon which we lay most emphasis, lasted six days, May 29 through June 3, 1913, Havens, Schneider, and

Sisco being the subjects. Five men participated in the last expedition, October 23 to 27, 1913. Two, Schneider and Sisco, ascended by railway-car, while Eager, Havens, and Munro walked from Manitou to the summit. In addition to the five persons mentioned above, H. H. Robison, the resident manager of the Summit House, also served as a subject. He has now spent eighteen seasons, each of about six months, on the summit of Pike's Peak.¹

THE FREQUENCY OF THE PULSE

Durig and Kolmer² give a critical review of the earlier studies of the pulse rate at high altitudes. They point out how greatly the heart rate varies with a variety of influences and they hold that the phenomena of circulation at high altitudes can be solved only when accidental influences are completely eliminated. Many discrepancies appear in the records of altitude studies. These are in a measure due to different conditions of living at the higher stations, such as restricted and unsatisfactory diet, poor ventilation, poor beds, and low room temperatures. Durig and Kolmer believe that circulation data obtained at low and high altitudes should be compared only in cases where the subject of observation has subsisted on a similar diet at the two altitudes and was reclining with muscles completely relaxed when under observation.

The majority of circulation records have been obtained on men who have undergone considerable physical exertion in climbing a mountain. All such records show that the heart rate increases decidedly during an ascent. Mosso³ counted the pulse rate of five soldiers each morning before they had risen and found that the rate on the summit of Monte Rosa never sank to the minimum observed in Turin. The differences noted by him are less than those found in many other records. The acceleration at the end

¹ We wish here to offer our hearty appreciation to Mr. LEONARD P. EAGER, Mr. LEON C. HAVENS, Mr. E. EVERETT MUNRO, and Mr. H. H. ROBISON for serving as subjects for experimentation and for kindly help. We also take this opportunity to express our sincere thanks to Mr. C. W. SELLS, President of the Manitou and Pike's Peak Railway; and to Mr. J. G. HIESTAND, proprietor of the Summit House, for generous help and many facilities granted.

² DURIG: *Physiologische Ergebnisse der im Jahre 1906 durchgeführten Monte Rosa Expedition*, p. 41.

³ MOSO: *Life of man on the High Alps*, 1899, pp. 66 and 213.

of their sojourn was 11.7, 25, 42.4, 43.4, and 85.6 per cent respectively. Zuntz and coworkers¹ give records, from which the following figures are obtained. Using the averages of the pulse rates at Brienz (1640 feet) and Rothorn (7052 feet) and the averages at Capanna Regina Margherita (14,965 feet) on the summit of Monte Rosa, we find the percentage of acceleration was for Caspari 20.3, Loewy 28.6, Zuntz 28.9, and Kolmer 36. On the last morning of their stay the increase was 8, 20, 20.3, and 33.3 per cent. Durig and Kolmer² the morning following the ascent of Monte Rosa from Col d'Olen (9360 feet) found the pulse rate to be for Rainer 97, Reichel 92, Durig 87, and Kolmer 80. With one exception, a further acceleration occurred for from one to three days. The maximum increase in pulse rate was, Rainer 74, Kolmer 50, Reichel 44, and Durig 30 per cent. After this the rate retarded considerably for each man, but never sank as low as the normal for each at sea-level. In the English-American Pike's Peak Expedition³ the pulse was not counted on the subject in bed so that these data are not wholly comparable with the above. There is, nevertheless, some similarity in events. These observations are of interest in view of our own work. The resting pulse, in the sitting position, in Douglas, Henderson, and Schneider progressively accelerated, not for three days, but for about a fortnight, after which it gradually became slower. Even after five weeks the rates were decidedly more rapid than the normals for sea-level. In Haldane the change was wholly different; the resting pulse from the first decreased until at the end of residence it was far below his sea-level rate.

The decrease in the pulse rate found in Haldane is exceptional. Mosso⁴ has reported that the two keepers of the Regina Margherita Hut had the same pulse rate at the end of the season as on the plain before ascending. We have found no cases of such return to normal, nor fall below normal, among the men who spend the summer working in the hotel on the summit of Pike's

¹ ZUNTZ, LOEWY, MÜLLER, and CASPARI: *Höhenklima und Bergwanderungen*, 1905, p. 337.

² DURIG: *loc cit.*

³ DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *Philosophical transactions of the royal society of London*, 1913, Series B, ciii, p. 262.

⁴ MOSO: *loc cit.*, p. 64.

Peak. In such persons the pulse rate, even after a residence of three and more months, has been above the normal for sea-level.

It is generally recognized that moderately high altitudes, 6000 to 9500 feet, do not in most persons cause an augmentation of the cardiac rate.

We have made a careful examination of the pulse rate in order to determine whether it is necessary for a subject to take the reclining posture with relaxed muscles in case the circulation data obtained at low and high altitudes are to be compared. For this purpose pulse counts were recorded frequently throughout the winter months in Colorado Springs and on the summit of Pike's Peak during the several expeditions.

The conditions under which we lived were quite similar at the two altitudes. The periods of observation on Pike's Peak had an atmospheric temperature variation corresponding to that of the winter in Colorado Springs. In the Summit House four rooms were placed at our disposal. The largest of these rooms, used as a laboratory, and from which each of the other rooms opened, was warmed with a stove so that the temperature was easily regulated. The beds were comfortable and clean. Our food included fresh meats, vegetables, and fruits, in fact the same variety that was to be had in Colorado Springs. The conditions of living, then, with the exception of barometric pressure, were practically the same at our two laboratories. Our physical exertion throughout was governed by the requirements of experimentation and was very similar at the two altitudes.

Pulse counts were made during the journey up the "Cog" railroad on each of us that went up by train. After equilibrium was once established the pulse rate remained constant throughout the journey and even on the summit, as we remained sitting quietly in the train after it had stopped, did not accelerate. The rates for the three of us May 29 were 60, 64, and 70. However, moderate exertion at once caused an extraordinary acceleration in pulse rate. Thus in one of us on October 12, 1912, after slowly carrying two moderately heavy suit cases 120 feet from the car to the Summit House, the pulse rate had augmented from 73 to 104. Again an hour later walking 350 paces at the rate of three miles per hour it accelerated from 80 to 120. The effect was not

so lasting as after the more vigorous exertion required to secure a similar increase at a low altitude. On the first day on Pike's Peak the return to normal after mild exertion required from two to five minutes. The acceleration for such mild work was less twenty-four hours later and marked improvement was noticed by the end of the second day.

The train on May 29 arrived at the summit at 11.25 in the morning. The members of that expedition began at once to slowly set up the apparatus, avoiding hurried movements. Throughout the day, whenever we were sitting, counts of the pulse were made. Havens' pulse continued at the tempo common for him in Colorado Springs, ranging between 60 and 78. Sisco showed more variation than ordinarily, but in the evening had counts of 65 and 67. Schneider throughout the afternoon retained on the whole his normal low altitude rate, but during the evening had an acceleration to between 85 and 90.

Schneider and Sisco each developed a headache during the first afternoon. Schneider later was mountain sick and his headache continued for several days. Sisco's headache was slight, continued throughout the first night, and wholly disappeared by noon of the thirtieth.

The pulse rates for each man of the May expedition taken in the morning before arising are given in full in the curves of Fig. I. On using the averages for the rates observed in Colorado Springs we find Havens had an acceleration of only 7.1 per cent the first morning. His heart rate was greater the second morning, had fallen the third, and reached its maximum, 21.4 per cent, the fifth or last morning. Sisco's heart had not clearly accelerated the first morning, but if the average of counts at the lower altitude is taken he showed an increase of 4.5 per cent. The rate was greater each succeeding morning and on his last had augmented 18.8 per cent. This rather moderate acceleration, which is in marked contrast with that observed by Durig and Kolmer, is accounted for by the fact that we ascended passively by train while they climbed the mountain on foot.

With Schneider the pulse changes were different; he was quite mountain sick throughout the first night. As a consequence his pulse had augmented by the first morning 46.6 per cent. Each

morning following it was found to be slower than on the day previous and by the fifth morning the rate was only 17.3 per cent above his normal.

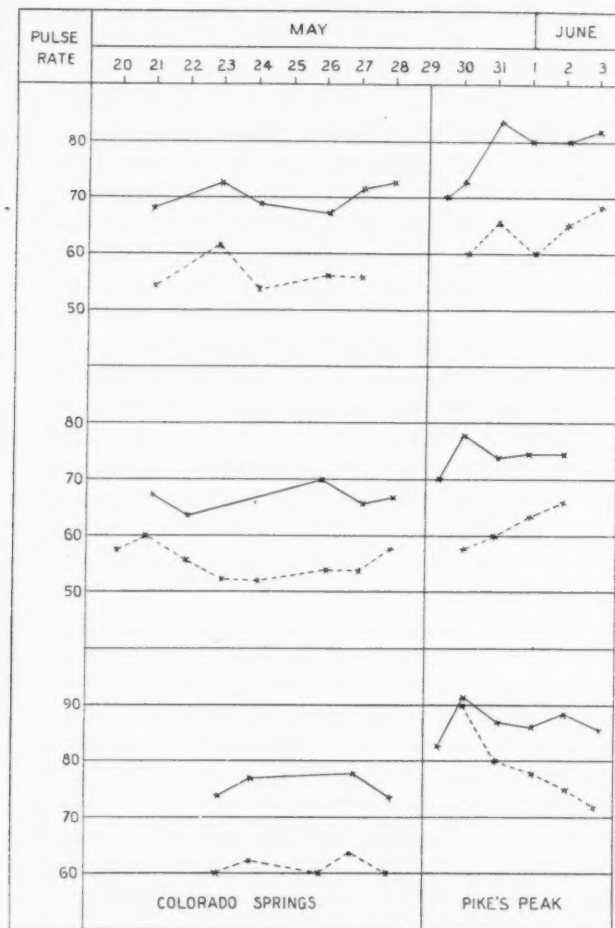


FIGURE 1

In the autumn expedition of 1913, only Schneider and Sisco of the party went up by train. Schneider, who had an average of 62 in Colorado Springs for the four mornings prior to the

ascent, had on Pike's Peak on each of the four mornings the following pulse rates: 88, 72, 74, and 76. Sisco had at the time of the ascent a slight bronchitis with no fever or other symptoms of illness. This condition was sufficient, however, to alter his reaction. Instead of a gradual daily increase in the rate, as observed in May, his heart rate had accelerated from an average of 50 in Colorado Springs to 66 the first morning, 67 the following morning, and had decreased to 62 the next two mornings.

After a residence of almost six months on the summit the pulse rate of Robison, while in bed, was exactly 64 on each of three consecutive mornings. This figure is above the rate noted in him a year earlier after his return to Colorado Springs from the summit.¹ It was then 60 for five mornings, even after he had walked to the college laboratories.

TABLE I
PULSE RATE WHILE SEATED

| | Havens | | Schneider | | Sisco | |
|-------------------------------|------------------|----------------|------------------|----------------|------------------|----------------|
| | Colo. Springs | Pike's Peak | Colo. Springs | Pike's Peak | Colo. Springs | Pike's Peak |
| Mean | 70 | 80 | 76 | 88 | 68 | 75 |
| Minimum | 56 | 60 | 64 | 78 | 58 | 60 |
| Maximum | 88 | 92 | 86 | 100 | 82 | 86 |
| Percentage daily variation | 57.1 | 53.3 | 34.4 | 28.2 | 41.4 | 43.3 |

It was important to determine whether the heart rate of the laboratory worker, doing at the high altitude the daily routine involved in this research, was more accelerated than at the lower altitude or only proportionately augmented, when contrasted with the reclining pulse rate; and whether the accidental variations throughout the day were different than at the lower altitude. In Fig. 1 the rate of pulse found to be the average daily mean has been given with the early morning rates for three subjects.

¹ See SCHNEIDER: This journal, 1913, xxxii, p. 300.

Also in Table I are contrasted the daily variations in heart rate at the two altitudes. Changes due to exercise are not included. It is evident that the heart of each man merely took a higher daily tempo on the summit of Pike's Peak; the daily mean resting pulse curve agrees in general with the curve of the early morning rate. The tables showing arterial and venous pressures also contain pulse rates which give the details of the variation. The percentage of acceleration in what we have designated as the daily mean was for Havens 14.3, Sisco 10.3, and Schneider 15.8. The percentage increase observed throughout the day was, therefore, somewhat less for each man than his early morning acceleration of the last day. Havens' heart did not accelerate the 29th. His mean pulse rate was 73 on the 30th, had increased to 84 on the 31st, and on the following days had decreased to 80. Schneider's mean was 91 on May 30, the day he was most ill with mountain sickness. On the following days it varied between 87 and 89. Sisco also showed the highest mean rate on the 30th when it reached 79. By the following day this was down to 75 where it remained for the balance of our sojourn on the summit.

During the October, 1913, sojourn Sisco's mean pulse rate was uniformly higher, 90 the 24th and 25th and about 80 the last two days. Schneider's mean was quite similar to his of the May trip.

The fluctuation in cardiac rate due to accidental and illy defined causes was, as shown in Table I in the percentage difference between minimum and maximum, practically the same at the two altitudes. These data are also from the expedition in May, at which time physical exertion constituted only a small part of a day's routine.

The above facts and the almost constant parallel in the pulse rates at the two altitudes, when conditions are similar, justify us, we believe, in placing in contrast the altitude data of other phenomena of circulation obtained from men leading a quiet life.

ARTERIAL PRESSURES

Reviews of the early literature dealing with arterial pressures have been given by one of us and Hedblom,¹ and by Durig and

¹ SCHNEIDER and HEDBLOM: This journal, 1908, xxiii, p. 90.

Kolmer.¹ The early records deal almost entirely with systolic pressure and fail to reveal a definite influence of high altitude in one direction; some show an increase, others no change, and still others a fall in the pressure. The same lack of uniformity appears in the data of the more recent publications.

Schneider and Hedblom reported observations made, with the Erlanger sphygmomanometer, on nine young men who climbed Pike's Peak March 27, 1907, and remained seven days on the summit. In eight of these men there was a fall in the averages of the systolic and diastolic pressures. In five the decrease was too slight to be of importance. On looking over their original notes we find that two of the men, who averaged a fall in the systolic pressure of 11 and 22 mm. respectively, had constantly a lower pressure than in Colorado Springs. The ninth man had uniformly a higher systolic pressure on the Peak and showed an average rise of 11 mm.

Durig and Kolmer employed in their expedition to Monte Rosa the Gaertner tonometer. Immediately after their arrival on the summit each man showed a marked decrease in the systolic pressure. The averages of the records of later days, however, give for three of the party an increase and for the fourth a slight fall in pressure. They conclude that in general the effect of high altitudes is to increase rather than decrease arterial pressures.

Fuchs,² making observations on himself on Monte Rosa with a Riva Rocci sphygmomanometer having a wide cuff, found a slight increase, average 3.22 mm., in pressure. Ward³ about the same time, in connection with another study on the same mountain, determined his systolic pressure, which during a sojourn of seven days averaged 106 mm. This is slightly below his sea-level average of 109 mm.

The English-American Pike's Peak Expedition⁴ employed a "Tycos" sphygmomanometer and concluded that while the sys-

¹ DURIG: *loc cit.*, p. 69.

² FUCHS: Sitzungsberichten der physikalisch-medizinischen Sozietät in Erlangen, 1908, xl, p. 224.

³ WARD: *Journal of physiology*, 1908, xxxvii, p. 381.

⁴ DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *loc cit.*, p. 262.

tolic pressures were somewhat less than under ordinary barometric pressure the differences were inconstant and so slight as to fall for the most part within the errors of observation. The diastolic pressure clearly varied only in one of the four members of that expedition and in him there was a distinct rise associated with a decided fall in the pulse pressure. These differences were, however, also inconstant.

The studies by clinical men dealing with the relation between barometric pressure and blood pressure in pulmonary tuberculosis also fail to agree. Thus Peters¹ and Bullock,² first working separately and later together³ near 6000 feet, claim that altitude raises the blood pressure, while Smith⁴ and Pomeroy,⁵ each working separately at about the same altitude, report a fall in systolic pressure.

Realizing that many factors in activity and diet may influence arterial blood pressure, as was shown by one of us and Hedblom, we have sought in this study to make certain that the condition of each subject in these respects was comparable at both altitudes. The determinations of pressures were made with Erlanger's sphygmomanometer. To detect the systolic pressure we used the abrupt separation of the ascending and descending strokes of the pulse record as recommended by Erlanger⁶ and at the same time noted the return of the pulse wave at the wrist. Determinations were always made in duplicate.

The number of determinations made has been too great to be recorded here in full. However, in order that the ordinary range of variations may be clear it has seemed best to give in detail, in tables II and IV, a part of the data obtained from each man.

The changes that occurred in the arterial pressures at the high altitude were surprisingly slight, in fact they were so slight that they fall for the most part within the errors of observation.

¹ PETERS: Archives of internal medicine, 1908, ii, p. 42.

² BULLOCK: Journal of the American medical association, June, 1909, p. 23.

³ PETERS and BULLOCK: Archives of internal medicine, 1913, xii, p. 456.

⁴ SMITH: Public health reports, 1911, xxvi, No. 51.

⁵ POMEROY: Studies of cardio-vascular diseases, reprinted from the interstate medical journal, 1911, p. 105.

⁶ ERLANGER: This journal, 1901, vi, p. xxii.

Havens, during the sojourn in May, showed a greater range in the variation of the systolic pressure and an occasional pressure 8 mm. above his maximum at the lower altitude. These differences, however, were not found during the October stay.

TABLE II
ARTERIAL AND VENOUS PRESSURES

Havens

| Date | Time | Room temperature | Pulse rate | Arterial pressures in mm. of Hg | | | Venous pressure in cm. of water | Place |
|---------|------------|------------------|------------|---------------------------------|-----------|-----------|---------------------------------|---------------|
| | | | | Systolic | Diastolic | Pulse | | |
| Mar. 6 | 5 P.M. | 21 | 66 | 118 | 90 | 28 | 18.2 | Colo. Springs |
| 11 | 4 " | 19 | 78 | 122 | 78 | 44 | 11.7 | |
| 13 | 11.30 A.M. | 21 | 84 | 118 | 90 | 28 | 7.4 | |
| Apr. 29 | 11.30 " | 22 | 56 | 115 | 87 | 28 | 10.2 | |
| 30 | 4.30 P.M. | 23 | 72 | 124 | 85 | 39 | 11.7 | Pike's Peak |
| May 6 | 2.20 " | 21 | 75 | 118 | 84 | 34 | 16.2 | |
| 14 | 3 " | 22 | 70 | 124 | 84 | 40 | 15.0 | |
| 20 | 2 " | 20 | 78 | 124 | 86 | 38 | 18.2 | |
| 21 | 2 " | 20 | 70 | 124 | 84 | 40 | 11.0 | |
| Average | — | — | 72 | 121 | 85 | 35 | 13.3 | |
| May 29 | 2.30 P.M. | 21 | 78 | 110 | 84 | 26 | 16.9 | |
| 30 | 10.20 A.M. | 20 | 78 | 122 | 86 | 36 | 9.9 | |
| 30 | 5 P.M. | 23 | 70 | 132 | 88 | 44 | 12.7 | |
| 31 | 8.20 A.M. | 24 | 92 | 120 | 90 | 30 | 5.1 | |
| 31 | 2.50 P.M. | 18 | 90 | 124 | 90 | 34 | 6.3 | |
| June 1 | 8.20 A.M. | 21 | 90 | 119 | 86 | 33 | 4.4 | |
| 1 | 5.30 P.M. | 21 | 76 | 132 | 94 | 38 | 13.4 | |
| 3 | 8 A.M. | 21 | 86 | 122 | 91 | 31 | 11.1 | |
| 3 | 11.50 " | 19 | 80 | 124 | 93 | 31 | 9.5 | |
| Average | — | — | 82 | 123 | 89 | 34 | 9.9 | |

TABLE II (Continued) — Schneider

| | | | | | | | | |
|---------|------------|----|-----|-----|----|----|------|------------------|
| Mar. 5 | 4 P.M. | 23 | 72 | 114 | 84 | 30 | 12.8 | Colo. Springs |
| 12 | 3 " | 19 | 78 | 120 | 85 | 35 | 10.9 | |
| Apr. 10 | 3.30 " | 19 | 72 | 122 | 88 | 34 | 13.9 | |
| 25 | 4 " | 24 | 77 | 114 | 82 | 32 | 16.8 | |
| 29 | 5 " | 22 | 78 | 118 | 80 | 38 | 19.1 | |
| 30 | 3.30 " | 23 | 77 | 120 | 82 | 38 | 14.7 | |
| May 6 | 11.30 A.M. | 20 | 68 | 122 | 90 | 32 | 15.2 | |
| 14 | 3.45 P.M. | 22 | 80 | 120 | 86 | 34 | 19.2 | |
| Average | — | — | 75 | 119 | 85 | 34 | 15.3 | |
| May 29 | 2.15 P.M. | 21 | 82 | 124 | 86 | 38 | 19.8 | Pike's Peak |
| 29 | 5.30 " | 21 | 80 | 128 | 90 | 38 | 14.0 | |
| 30 | 10.40 A.M. | 21 | 88 | 123 | 88 | 35 | 13.3 | |
| 30 | 3 P.M. | 22 | 100 | 138 | 94 | 44 | 20.6 | |
| 31 | 7.10 A.M. | 27 | 81 | 130 | 96 | 34 | 13.7 | |
| June 1 | 8.50 " | 21 | 86 | 120 | 86 | 34 | 16.7 | |
| 1 | 5 P.M. | 21 | 82 | 116 | 86 | 30 | 15.5 | |
| 2 | 6.30 A.M. | 18 | 86 | 116 | 84 | 32 | 17.1 | |
| 2 | 12 noon | 21 | 94 | 114 | 82 | 32 | 8.3 | |
| 3 | 8.40 A.M. | 23 | 90 | 116 | 85 | 31 | 17.3 | |
| Average | — | — | 87 | 123 | 88 | 35 | 15.6 | |
| Sisco | | | | | | | | |
| Mar. 5 | 3 P.M. | 23 | 70 | 114 | 84 | 30 | 6.2 | Colo. Springs |
| Apr. 10 | 4 " | 19 | 74 | 122 | 85 | 37 | 7.2 | |
| 25 | 4.30 " | 25 | 68 | 112 | 84 | 28 | 9.0 | |
| 29 | 5.20 " | 22 | 60 | 120 | 80 | 40 | 8.5 | |
| 30 | 4 " | 23 | 78 | 114 | 86 | 28 | 10.4 | |
| May 6 | 4 " | 21 | 66 | 114 | 88 | 26 | 8.6 | |
| 8 | 4.15 " | 21 | 62 | 118 | 84 | 34 | 9.8 | |
| 22 | 11 A.M. | 19 | 70 | 126 | 84 | 42 | 8.2 | |
| Average | — | — | 69 | 118 | 84 | 33 | 8.5 | |

The Circulation of the Blood at High Altitudes

13

TABLE II (Continued)

Sisco (Continued)

| Date | Time | Room temperature | Pulse rate | Arterial pressures in mm. of Hg | | | Venous pressure in cm. of water | Place |
|--------------|------------|------------------|------------|---------------------------------|-----------|-----------|---------------------------------|---------------|
| | | | | Systolic | Diastolic | Pulse | | |
| May 29 | 2 P.M. | 21 | 86 | — | — | — | 11.4 | Pike's Peak |
| 29 | 4.30 " | 21 | 70 | 120 | 86 | 34 | 11.6 | |
| 30 | 10 A.M. | 20 | 70 | 110 | 84 | 26 | — 0.6 | |
| 30 | 3.30 P.M. | 20 | 80 | 116 | 85 | 31 | 1.5 | |
| 31 | 9 A.M. | 23 | 80 | 114 | 83 | 31 | 2.1 | |
| May 31 | 4 P.M. | 20 | 72 | 120 | 88 | 32 | — 0.2 | Pike's Peak |
| June 1 | 8 A.M. | 21 | 82 | 118 | 84 | 34 | — 0.7 | |
| 1 | 5.20 P.M. | 21 | 72 | 120 | 88 | 32 | 2.1 | |
| 2 | 6.45 A.M. | 21 | 76 | 116 | 80 | 36 | 0.9 | |
| 2 | 2 P.M. | 21 | 80 | 112 | 78 | 34 | 1.8 | |
| Average | — | — | 77 | 116 | 84 | 32 | 3.0 or (0.9) | |
| <i>Eager</i> | | | | | | | | |
| Oct. 13 | 3.40 P.M. | 20 | 81 | 116 | 84 | 32 | 14.5 | Colo. Springs |
| 17 | 11.40 A.M. | 21 | 72 | 128 | 88 | 40 | 15.0 | |
| 18 | 3.30 P.M. | 20 | 82 | 108 | 82 | 26 | 10.4 | |
| Nov. 20 | 9.45 A.M. | 21 | 84 | 126 | 84 | 42 | 11.0 | |
| Dec. 2 | 12.25 P.M. | 17 | 82 | 114 | 84 | 30 | 11.9 | |
| 5 | 10.55 A.M. | 19 | 84 | 126 | 82 | 44 | 12.6 | Pike's Peak |
| 15 | 1.55 P.M. | 19 | 86 | 126 | 88 | 38 | 15.0 | |
| Average | — | — | 82 | 121 | 86 | 36 | 12.9 | |
| Oct. 24 | 8 P.M. | 23 | 96 | 118 | 84 | 34 | 3.6 | |
| 25 | 9 A.M. | 20 | 100 | 106 | 78 | 28 | 8.2 | |
| 26 | 9 " | 23 | 96 | 114 | 82 | 32 | 9.2 | |
| 27 | 10 " | 16 | 87 | 116 | 87 | 29 | 1.5 | |
| Average | — | — | 95 | 114 | 83 | 31 | 5.6 | |

TABLE II (Continued)

Munro

| | | | | | | | | |
|---------|------------|----|-----------|------------|-----------|-----------|-------------|------------------|
| Oct. 7 | 11.25 A.M. | 19 | 84 | 122 | 90 | 32 | 9.7 | Colo. Springs |
| 10 | 4.35 P.M. | 20 | 74 | 116 | 78 | 38 | 15.0 | |
| 20 | 2.30 " | 16 | 78 | 116 | 84 | 32 | 15.4 | |
| Nov. 20 | 10.10 A.M. | 21 | 72 | 116 | 89 | 32 | 11.7 | |
| 26 | 10.45 " | 19 | 72 | 118 | 82 | 36 | 14.8 | |
| 27 | 11.45 " | 21 | 82 | 118 | 84 | 34 | 15.0 | |
| Average | — | — | 77 | 118 | 85 | 34 | 13.6 | Pike's Peak |
| Oct. 24 | 8.30 P.M. | 23 | 88 | 118 | 86 | 32 | 4.4 | |
| 25 | 8.50 A.M. | 20 | 100 | 114 | 82 | 32 | 6.9 | |
| 26 | 8.50 " | 24 | 95 | 122 | 89 | 33 | 2.6 | |
| 26 | 9.30 " | 24 | 94 | 118 | 82 | 36 | — 1.4 | |
| 27 | 6.45 " | 14 | 84 | 117 | 89 | 28 | — 4.2 | |
| Average | — | — | 92 | 118 | 86 | 32 | 1.7 | |

Schneider was, it will be recalled, mountain sick during the first days of the spring expedition and it was during those days, the first three, that the arterial pressures averaged unusually high: systolic 129, diastolic 91, and the pulse pressure 38. The averages for the three days show the following increase over the Colorado Springs averages: the systolic 10 mm., diastolic 6 mm., and pulse pressure 4 mm. However, on the morning of the fourth day there was a marked fall in his pressure and throughout the remainder of the stay the systolic and pulse pressures were each slightly below his Colorado Springs averages. During the October trip Schneider was ill only the first night and with this better health there failed to develop the early period of high pressure; his arterial pressures then conformed throughout the stay with those found to occur at the lower altitude. Observations made on Schneider with a "Tyco's" sphygmomanometer by the English-American Pike's Peak Expedition in 1911 show a 5 mm. fall in his average systolic pressure and 7 mm. decrease in the pulse pressure. With him then, when in health, it seems established that at the altitude

of 14,000 feet the arterial pressures are practically unchanged or at the best only slightly lowered.

Eager, who was one of the three to walk up the Peak, showed on the mountain an average decrease of 7 mm. in the systolic and 5 mm. in the pulse pressure but no change in the diastolic pressure.

In Munro and Sisco (during his first trip) we could find no constant change in any of the three pressures while they were on Pike's Peak. Sisco had in the October expedition a slight decrease in the systolic and pulse pressures.

TABLE III

AVERAGE ARTERIAL AND VENOUS PRESSURES FOR THE FOUR PERIODS

| Person | Period | Place | Pulse rate | Arterial pressures in mm. of Hg | | | Venous pressure in cm. of water |
|-----------|---------------|---------------|------------|---------------------------------|-----------|-------|---------------------------------|
| | | | | Systolic | Diastolic | Pulse | |
| Havens | Feb. 1-May 21 | Colo. Springs | 67 | 120 | 86 | 34 | 12.8 |
| " | May 29-June 3 | Pike's Peak | 83 | 122 | 89 | 33 | 9.9 |
| " | Oct.-Dec. | Colo. Springs | 74 | 126 | 90 | 36 | 12.4 |
| " | Oct. 23-27 | Pike's Peak | 87 | 125 | 92 | 33 | 9.8 |
| Schneider | Feb. 1-May 21 | Colo. Springs | 73 | 118 | 84 | 34 | 16.2 |
| " | May 29-31 | Pike's Peak | 88 | 129 | 91 | 38 | 15.7 |
| " | June 1-3 | " " | 86 | 116 | 85 | 31 | |
| " | Oct.-Dec. | Colo. Springs | 76 | 121 | 85 | 36 | 15.4 |
| " | Oct. 23-27 | Pike's Peak | 86 | 118 | 85 | 34 | 14.5 |
| Sisco | Feb. 1-May 21 | Colo. Springs | 66 | 118 | 85 | 33 | 8.9 |
| " | May 29-June 3 | Pike's Peak | 75 | 117 | 84 | 33 | 2.5 |
| " | Oct.-Dec. | Colo. Springs | 70 | 119 | 86 | 33 | 7.2 |
| " | Oct. 23-27 | Pike's Peak | 90 | 115 | 85 | 30 | 1.4 |

In Table III are given the averages of all normal arterial pressures obtained from Havens, Schneider, and Sisco for the two periods of observation in Colorado Springs and for the last

two expeditions up the Peak. There is a remarkable likeness in the data for the two periods at each altitude. What differences occur are on the whole slight and, appearing as they do in the readings at both altitudes, suggest that these are incidental and not the effect of altitude.

Since the two sets of pressure determinations for Havens, Sisco, and Schneider are in such complete agreement for the two sojourns on Pike's Peak, we feel we are justified in concluding that we have succeeded in eliminating disturbing factors and that the conditions of life were, excepting barometric pressure, practically the same at the low and high altitudes.

The observations on Robison, given in Table IV, are of more than passing interest in that he spends six months of each year on the summit. Schneider¹ has recently shown that during a period of six years in which Robison has been under observation his arterial pressure has remained normal. A few of our determinations were made last spring before Robison ascended the Peak. When these are contrasted with the pressures obtained on the mountain the high altitude readings show an average fall of 6 mm. in each of the systolic and pulse pressures, but no change in his diastolic pressure. The decrease observed in the pulse pressure is in harmony with our recoil curve records in which we find the recoil for him less than that of the other subjects of our investigation.

These data from Robison are in complete agreement with those obtained on him by Schneider and Hedblom² in 1907. They record a series of eighteen observations in which his systolic pressure had on Pike's Peak an average decrease of 7 mm. and pulse pressure 5 mm.

There are among the records of this laboratory arterial pressure determinations on five employees of the hotel who have resided from ten days to several months on the summit of the Peak. For these men the systolic pressure ranges from 104 to 134, the diastolic from 75 to 90, and the pulse pressure from 26 to 50 mm.

Data accumulated during the past five years from determina-

¹ SCHNEIDER: This journal, 1913, xxxii, p. 299.

² SCHNEIDER and HEDBLOM: *loc. cit.*, p. 101, Table VI.

tions on ninety young men of college age show that for about 80 per cent the average systolic pressure at an altitude of 6000 feet is less than 120 mm. Our experience leads to the opinion that at an altitude of 6000 feet normal healthy young men show the same range and distribution of pressures as young men do at sea-level.

TABLE IV
ARTERIAL AND VENOUS PRESSURES. (ROBISON)

| Date | Time | Room temperature | Pulse rate | Arterial pressures in mm. of Hg | | | Venous pressure in cm. of water | Place |
|---------|------------|------------------|------------|---------------------------------|-----------|-------|---------------------------------|---------------|
| | | | | Systolic | Diastolic | Pulse | | |
| Jan. 28 | 7.30 A.M. | — | 76 | 116 | 84 | 32 | — | Colo. Springs |
| 30 | 8.00 " | — | 70 | 114 | 80 | 34 | — | |
| May 1 | 7.45 " | 21 | 66 | 114 | 84 | 30 | 13.3 | |
| 1 | 9.35 " | 21 | 66 | — | — | — | 15.7 | |
| Nov. 23 | 11.45 " | 19 | 77 | 118 | 82 | 36 | 11.8 | |
| Average | — | — | 71 | 116 | 83 | 33 | 13.6 | Pike's Peak |
| May 31 | 10.00 A.M. | 18 | 90 | 110 | 84 | 26 | 13.9 | |
| 31 | 5.30 P.M. | 21 | 84 | 106 | 80 | 26 | 7.9 | |
| June 1 | 9.00 A.M. | 21 | 86 | 110 | 84 | 26 | 12.5 | |
| 1 | 5.40 P.M. | 21 | 81 | 114 | 84 | 30 | 4.0 | |
| 3 | 9.10 A.M. | 22 | 96 | 112 | 84 | 28 | 11.2 | |
| Average | — | — | 87 | 110 | 83 | 27 | 9.9 | |

Of special interest are the data on pulse pressure, the difference between systolic and diastolic arterial pressure, which is generally taken as evidence of the volume of the systolic discharge or the size of the heart strokes. Our own data and those of Douglas, Haldane, Henderson, and Schneider indicate that in the majority of persons the pulse pressure does not definitely alter at high altitudes and in those in which a change occurs there will be a slight decrease in the output of the heart.

We conclude, from our experience in these several expeditions and from the data accumulated in this laboratory during the past six years, that for many, and very likely the majority of healthy men, residence at very high altitudes does not influence the arterial pressures. In a certain, but as yet undetermined, percentage of men it will cause a demonstrable fall in the systolic and pulse pressures, and in very exceptional cases will bring about a marked rise in the arterial pressures. This rise was observed by Schneider and Hedblom in one man.

VENOUS PRESSURE

For the determination of venous pressure we have constructed an instrument which is a modification of the one described by Hooker and Eyster.¹ Experience with two of the Hooker-Eyster instruments made here demonstrated that the rectangular form of the box is a difficult one over which to fit the rubber dam by means of the metal collar. Only after repeated trials was it possible to secure an air-tight chamber and this would hold only a few days; in that time the rubber skirt would be cut at the angles by the collar.

Our instrument² is a cylindrical glass box 5 cm. in diameter and 1.8 cm. in height. The top is a thin watch-glass cemented to a narrow thin metal band which in turn is cemented to the glass cylinder. The metal band has a tube entering it which connects the chamber with a manometer and also has attachments for the binding tapes which hold the instrument in place on the arm. Over the lower end of the cylinder a thin metal band is cemented and a metal collar 4 mm. wide holds the rubber sheet in place. The rubber sheet is easily placed in position, and should leaks occur around the band these are readily closed with rubber cement or balsam, after which the instrument is ready for constant use for several months or until the rubber deteriorates.

For use a rectangular opening is cut in the rubber covering of the bottom. The box, after the plan employed by Hooker and

¹ HOOKER and EYSTER: Johns Hopkins hospital bulletin, 1908, xix, p. 274.

² We are indebted to Mr. E. E. TALIAFERRO for suggestions and for making our instrument.

Eyster, is connected with a water manometer and rubber pressure bulb so that the pressure is transmitted directly to the box and manometer. The instrument can readily be placed on the arm or hand in such a manner that it does not exert pressure on the veins.

Our determinations of the venous pressure have all been made with the above instrument on the back of the hand or wrist. Pressure was applied rapidly until the vein collapsed and the manometer was then read by an assistant or the subject of experimentation. Pressure was next lowered and again applied and this repeated until ten or fifteen readings had been made. The average of these readings was then taken and a correction made by deducting the difference in level between the vein and the right auricle of the heart. This level of the heart was considered to be the mid point at the anterior-posterior diameter of the body at the tip of the sternum, the subcostal angle, the point arbitrarily chosen by v. Rechlinghausen.¹

We have not to date determined the venous pressure of many different individuals. A limited number of observations on seventeen men indicate that the pressure range at 6000 feet is about the same — 2 to 16 cm. of water — as Hooker² found in Baltimore. An occasional reading, for which an explanation was not apparent, has been as high as 20 cm.; but in not a single case has this high pressure been found to be the normal condition for an individual. Since the number of individuals examined has been so small and on several of the men only one and two determinations have been made, we give only a tentative estimate of the average value of the venous pressure in Colorado Springs, which, with our instrument, we find to lie between 10 and 11 cm. of water. Hooker gives 9 cm. as the average value near sea-level. This difference in view of experience on Pike's Peak cannot be attributed to altitude influence but rather to instrumental and technic differences.

Venous pressures have not been studied heretofore at extremely high altitudes. Oliver³ made observations on two subjects, aged

¹ V. RECHLINGHAUSEN: *Archiv für experimentelle Pathologie und Pharmacologie*, 1906, lv, p. 463.

² HOOKER: *This journal*, 1911, xxviii, p. 235.

³ OLIVER: *Blood and blood pressure*, 1901, p. 204.

23 and 57, on a visit to Arosa, altitude 5800 feet, finding their venous pressures high. He fails to give data. Sewall¹ finds evidence of overstrain of the right side of the heart in certain cases newly arrived in Denver (5300 feet) from lower levels, from which he concludes that the venous pressure at least in such cases is abnormally high. However, his determinations on healthy men with an instrument designed by himself² show an average pressure of about 4 mm. Hg. This is below the average for near sea-level as given by Hooker.

A part of the data on venous pressure secured in our expeditions to Pike's Peak appears in tables II, III, and IV. They show a decided fall in this pressure for Eager, Havens, Munro, and Sisco, but no change for Schneider. The percentage of the fall in the averages of the venous pressure on Pike's Peak was for Munro 87, Sisco 72, Eager 57, and Havens 25. Individual differences were in evidence. Sisco during the first half day on the summit had on both sojourns a high venous pressure; in the first instance it was above that of any determination made in Colorado Springs. During the first night on the summit his pressure lowered and frequently thereafter was slightly negative; at one time it was 3 cm. below atmospheric pressure. Munro likewise often showed a negative venous pressure; once this was fully 4 cm. The highest pressure obtained on Havens occurred the first half day of the first expedition. His venous pressure was more variable than that of any other of our subjects. He generally had a higher pressure in the morning than in the afternoon.

The averages of the venous pressures for Havens, Schneider, and Sisco for the two expeditions appear in Table III. The changes observed the second trip almost duplicate those of the spring expedition.

The observations on Robison (see Table IV), who spends six months of each year on the summit of Pike's Peak, show his venous pressure to fluctuate as did Havens'. It should be noted that this pressure for him was always higher in the morning than in

¹ SEWALL: Transactions of the American climatological association, 1906, xxii, p. 122.

² SEWALL: Journal of the American medical association, 1906, xlvii, p. 1279.

the afternoon; in fact in the morning it was as high as in Colorado Springs. Only a small number of determinations have been made on Robison in Colorado Springs, but they average more than his average pressure on Pike's Peak. This average shows a fall of 27 per cent on the Peak.

While on Pike's Peak the venous pulse was noted on three of us in the recumbent position. Since we were not equipped for recording this pulse we were compelled to note only the visible changes. In Havens and Schneider the external jugular veins appeared as full and the pulse as pronounced as at the lower altitude. With Sisco in the reclining position at a time when the venous pressure was -0.8 the jugulars were visible and the pulse fairly distinct. A rock weighing about 25 lbs., then placed on Sisco's abdomen, raised his venous pressure to 1.6 cm. and somewhat accentuated the venous pulse. This observation demonstrated that the splanchnic reservoir at the high altitude did not contain more blood than at the altitude of Colorado Springs, since there we had been able to increase the venous pressure a little over 4 cm. with a similar weight.

The venous pressure, as shown by Krogh¹ and by Henderson and Barringer² determines the extent of filling of the right ventricle and is thus the principal factor controlling the volume of the arterial blood stream. It may be questioned whether men with as low a venous pressure as was sometimes found in Munro and Sisco on Pike's Peak do not have a greatly reduced systolic discharge. A study of sphygmograms and of our recoil-board curves do not indicate such a reduction. Furthermore, Henderson and Barringer³ have shown that a venous pressure above that which they designate as the critical venous pressure will not increase the diastolic filling of the ventricle; i.e., the heart will begin to beat with an efficiency which is maximal for a given rate when the critical venous pressure is reached. They find that the critical venous pressure necessary to distend the dog's right ventricle as rapidly as it relaxes is not more than 50 mm. of saline. They deem it probable that in the adult human heart the larger

¹ KROGH: *Skandinavisches Archiv für Physiologie*, 1912, xxvii, p. 227.

² HENDERSON and BARRINGER: *This journal*, 1913, xxxi, p. 288.

³ HENDERSON and BARRINGER: *loc. cit.*, p. 352.

size involves a somewhat greater critical pressure, but consider that the negative pressure of the chest would provide an effective pressure of at least the critical value. The normal intrathoracic negative pressure in expiration at sea-level is at least -60 mm. of water and in inspiration -100 mm. or more. The thoracic negative pressure must average somewhat higher at extreme altitudes in that the depth of inspiration is increased, it having been shown by Douglas, Haldane Henderson, and Schneider¹ that the rate and depth of breathing on Pike's Peak is such as to cause the inhalation of 30 per cent more air per minute. Since the rate of respiration is only slightly or not at all increased it follows that the depth will increase and with it the negative pressure. Furthermore, the lessened atmospheric pressure very likely leads to greater negative pressure even during expiration. Whatever the average negative intrathoracic pressure may be on Pike's Peak it is possible that there may occur periods of such low venous pressure in some men, examples Munro and Sisco, that for a time this pressure is below the critical venous pressure. This condition, however, is only occasional in men so far examined. In the majority of men the venous pressure is always positive and even in those in which it is at times negative it is the greater part of the day positive; hence it follows that the venous supply and pressure are generally sufficient at the high altitude to give a maximal efficiency of heart stroke.

The cause of the fall in the venous blood pressure at the high altitude appears to be the increased rate of the heart beat, which permits an increased outflow from the large veins. The probable decrease in intrathoracic pressure may also be a supplementing factor. That diminution of ventricular output was not responsible for the fall in venous pressure was evidenced by our recoil-board records, in which the height of the curves were practically the same at both altitudes; that it was not due to a stagnation of the blood in the splanchnic reservoir was shown by pressing the blood from this area into the systemic or external circulation by means of weights placed on the abdomen of men in the reclining position, since in each man this increase in pressure was no greater than that secured in Colorado Springs; that it was not caused

¹ DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *loc. cit.*, p. 217.

by a contraction of the arterioles was proven by the fact that the arterial pressures were not increased, also by the fact that the capillary pressures were practically unaltered.

CAPILLARY PRESSURES

For these determinations we employed a Lombard pressure chamber which we had constructed in accordance with his specifications.¹ With this instrument the skin is wet with glycerine and the smaller blood vessels are viewed with a microscope as the pressure is applied. The obliteration of the blood vessel is observed rather than the blanching of the skin as in older methods. We eliminated the Wolf-bottle suggested by Lombard for applying pressure and employed instead the same device that was used with the venous pressure apparatus. A Nernst lamp was the source of illumination in Colorado Springs while on the summit of Pike's Peak it became necessary to use sunlight which was reflected onto the microscopic field by means of a mirror.

Unfortunately adequate light could not be obtained in the laboratory on the summit so that the capillary readings on the mountain had to be made out of doors. This made it impossible to regulate the temperature so that conditions would be similar to those experienced at the lower altitude. Sheltered places were found near the Summit House, but even then the temperatures were much below those in the laboratory. Because of this and frequent cloudy weather the number of determinations on the Peak was much limited.

The capillary determinations which have been corrected for the intercostal angle appear in Table V. The most compressible capillaries disappeared at fully as low pressures on Pike's Peak as in Colorado Springs. To obliterate the majority of capillaries required for Havens and Sisco a slightly greater pressure on the Peak than was usually necessary in Colorado Springs, but was not above pressures often found at the lower altitude. For Schneider in one trial the majority of capillaries disappeared at the same pressure as the average in Colorado Springs, but in the second determination on another day it was above this average. The

¹ LOMBARD: This journal, 1912, xxix, p. 347.

most resistant capillaries were obliterated by pressures of 67 mm. Hg and under. Our readings both in Colorado Springs and on Pike's Peak fall within the ranges of variation established by Lombard for near a sea-level altitude. He found the pressures

TABLE V
CAPILLARY PRESSURES

| Subject | Place | Reading | Pressures in mm. of Hg | | |
|-----------|---------------|---------|------------------------|-------------------------|----------------|
| | | | First capillaries | Majority of capillaries | Last capillary |
| Havens | Colo. Springs | Average | 21 | 37 | 56 |
| " | " " | Lowest | 14 | 30 | 44 |
| " | " " | Highest | 27 | 52 | 63 |
| " | Pike's Peak | May 31 | 21 | 47 | — |
| " | " " | 31 | 21 | 42 | — |
| " | " " | June 2 | 12 | 44 | 67 |
| Schneider | Colo. Springs | Average | 24 | 39 | 54 |
| " | " " | Lowest | 18 | 33 | 48 |
| " | " " | Highest | 31 | 43 | 67 |
| " | Pike's Peak | May 31 | 17 | 37 | — |
| " | " " | June 2 | 19 | 50 | 66 |
| Sisco | Colo. Springs | Average | 26 | 42 | 58 |
| " | " " | Lowest | 16 | 30 | 54 |
| " | " " | Highest | 38 | 53 | 61 |
| " | Pike's Peak | May 31 | 27 | 48 | — |
| " | " " | June 2 | 16 | 46 | 60 |

in millimeters of mercury to vary for the most compressible capillaries between 15 and 25, the average capillaries 35 to 45, and the most resisting capillaries 60 to 70.¹

¹ LOMBARD: *loc. cit.*, p. 362.

According to Hough,¹ also Oliver,² low temperatures (from 5° to 15° C.) increase capillary pressure by causing a venous constriction. Our determinations on Pike's Peak were out of doors under a temperature of 10° while those in Colorado Springs were at temperatures varying from 17° to 22° C. This, applied to our data, suggests that the capillary pressure on Pike's Peak at ordinary room temperatures would be at least the same or slightly less than in Colorado Springs. Bayliss and Starling³ have shown, when the capillary pressure cannot be measured directly, that simultaneous determinations of arterial and venous pressures will give reliable information as to the variation of capillary pressure; that in cases in which one of these falls while the other remains constant the capillary pressure must be diminished, and in cases where arterial and venous pressures rise or fall together the capillary pressure rises or falls with them. From our arterial and venous determinations we are, therefore, warranted in concluding that the capillary pressure is decreased in some men and unaltered in others by residence at high altitudes.

It has frequently been claimed that bleeding from nose, lips, gums, lungs, or stomach is a common experience at high altitudes and this has been attributed to increased capillary pressure. Among the thousands of people that one of us has seen ascend Pike's Peak there have been very few cases of hemorrhages and these of the nose only. Such cases are so rare that doubt would be thrown on the usual explanation even in the absence of the positive proof that capillary pressure is not increased.

THE MASS-MOVEMENT OF THE BLOOD SHOWN BY A RECOIL CURVE

The device employed has been described by Yandell Henderson⁴ and was used by the English-American Pike's Peak Expedition.⁵ A plank, or recoil board, was supported upon rubber stoppers, a large and a medium size stopper placed one upon the

¹ HOUGH: This journal, 1900, iii, p. xii.

² OLIVER: Studies in blood pressure, 1908, p. 77.

³ BAYLISS and STARLING: Journal of physiology, 1894, xvi, p. 159.

⁴ YANDELL HENDERSON: This journal, 1905, xiv, p. 290.

⁵ DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *loc. cit.*, p. 267.

other under each corner. By means of a small upright of wood a stiff wire hook was connected with a lever in such a manner that the movements of the board were magnified sixty times and recorded upon a smoked drum. The amplitude of the graphic record affords an index of the volume of blood propelled by each heart stroke in relation to the body weight.

Since our curves are similar to those obtained by Douglas, Haldane, Henderson, and Schneider, and our results in complete agreement with their work, they are here omitted. The amplitude of the curve varied on the whole with the pulse pressure, and the variations were practically the same at the low and high altitudes. The amplitude of the curve for Robison was uniformly less than that of the other subjects. Unfortunately no records are available for him at the lower altitude. It is, however, of interest to find his pulse pressure also less at the high altitude. When the heart rate reached a hundred and over there was as a rule a reduction in the amplitude of the curve.

It is evident from our observations on the pulse, the recoil curve, and the various pressures that in the men examined the conditions were favorable for an increase in the rate of blood flow while they were on the summit of Pike's Peak. The amplitude of the heart beat, as shown by the pulse pressure and recoil curve, was practically unaltered in four of the six men examined. In the two exceptions the pulse pressure showed a diminution of 14 and 18 per cent. Each subject examined had a marked acceleration, 10 to 21 per cent, in heart rate on the Peak, the greatest occurring in the case of greatest fall in pulse pressure. If the pulse rate be multiplied by the pulse pressure and the product be taken as a relative measure of the volume of the blood stream per minute, for each subject a marked increase in the circulation rate is indicated. The output of the heart per minute being increased without a corresponding rise in the arterial systolic pressure, a readjustment in the peripheral resistance, i.e., the arterioles, must occur so as to permit a more abundant flow of blood through the capillaries. The arterial systolic pressure was unchanged in four of our subjects and lowered in two, thus indicating that such readjustment did occur. Furthermore, in all but one

man a lowering of the venous pressure was found, thus giving another factor favoring an increase in the rate of circulation. With the physiologic resistance in the circuit decreased, or even remaining unaltered, a fall in pressure at the outflow end can only give an increase in the velocity of flow.

SUMMARY

1. The pulse rate does not accelerate immediately on arrival at an altitude of 14,109 feet, but requires several days to reach its maximum. Very moderate exertion at first brings on an extraordinary, but brief, acceleration, an effect which is less marked by the second or third day. In mountain sickness the rate augments rapidly, to retard on recovery to high altitude normal. The daily mean pulse rate for a subject in the sitting posture while rapid, shows approximately the same proportionate increase as the early morning rate does when compared with rates at the lower altitude. The daily fluctuation of heart rate due to accidental and illy defined causes was found to have approximately the same percentage range at low and high altitudes.

2. In the majority of healthy men at high altitudes the arterial pressures are unchanged. Some men may experience a moderate decrease in the systolic and pulse pressure, the diastolic remaining most constant. In about 80 per cent of young men of college age at the altitude of 6000 feet the normal systolic pressure is under 120 mm. Hg.

3. Venous pressure determinations, made with a new form of instrument, show the pressure at an altitude of 6000 feet to vary from 2 to 16 cm. of water, the range of variation recorded by Hooker for sea-level. In five out of six subjects on Pike's Peak the venous pressure was lowered from 25 to 87 per cent. In two men it was at times slightly negative.

4. The capillary pressure was not clearly altered by reduced barometric pressure.

5. A study of the mass-movement of the blood by the recoil-board method and observations on the pulse pressure show the volume of ventricular output per heart stroke to be the same for four of the men at both altitudes and to be clearly reduced for one man at the high altitude.

6. In consequence of the increased pulse rate and fall in venous pressure and the unchanged or only slightly lowered arterial pressure, conditions of the vascular system favor an increased rate of blood flow on Pike's Peak. An adaptive response in the mechanism regulating the peripheral resistance is predicated.

THE CIRCULATION OF THE BLOOD IN MAN AT HIGH ALTITUDES

II. THE RATE OF BLOOD FLOW AND THE INFLUENCE OF OXYGEN ON THE PULSE RATE AND BLOOD FLOW

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THE data here presented have been obtained from the same men who served as subjects in our study of the pulse rate, arterial, capillary, and venous pressures.¹ Three men participated in the first expedition (May 29-June 3), while these and two additional men were members of the last expedition (October 23-27, 1913) to the summit of Pike's Peak. A sixth subject was the resident manager of the Summit House.

BLOOD FLOW IN THE HANDS

We have sought throughout our study to determine how and to what extent the circulation rate is altered by residence at very high altitudes. Naturally the best way to settle the question would be a direct determination of the volume of the systolic discharge per minute into the aorta. Unfortunately no simple method has as yet been devised that will even indirectly give satisfactory data as to the volume of the heart output in man. Since the oxygen-want at high altitude stimulates the blood-forming centers to increase the percentage and the total amount of hemoglobin in the blood, the lungs to actively secrete oxygen, and the respiratory mechanism to a greater ventilation of the lungs, all so that the tissues may be more adequately supplied with oxygen; it has seemed almost certain that the rate of blood flow must also be increased for the same purpose. A more rapid

¹ See this journal, 1914, xxxiv, p. 1.

rate of blood flow could raise to a limited extent the oxygen pressure in the blood passing through the tissues and so ensure better oxidation within the tissues. The problem then to be solved is not so much the amount of the systolic discharge but rather the relative rate of the blood flow through any organ or tissue at low and high altitudes. We have, therefore, made determinations of the amount of blood flow in the hands.

The determinations of the blood flow were made by Stewart's¹ method. For this purpose we constructed and equipped two hand-calorimeters according to his specifications. The method determines the amount of heat given off by the resting hand in a given time, and indirectly the temperatures of the arterial and venous blood in the part. With these data it is possible to calculate how much blood has passed through the hand in order that it might give off the determined amount of heat. The method undoubtedly gives values of blood flow somewhat less than the amount actually passing through the hand. It is, nevertheless, a simple method which measures the rate with a considerable degree of accuracy and has served well in our problem in which evidence as to change in the rate of the flow was demanded.

Experience early showed us that muscular activity of any kind accelerates the blood flow. Hence in our study we have made determinations after the subject had been quiet for several hours and as often as possible on days in which he had not indulged in strenuous work or exercise. The conditions of the subject and of experimentation correspond at the two altitudes. It was impossible to have an absolutely uniform room temperature throughout. However, Hewlett² has shown that room temperatures between 18 and 25.5° C. do not materially alter the blood flow in the arm. With but one exception our room temperatures fell within this range.

In all experiments the subject was required to immerse the hands for at least ten minutes in a bath of the same temperature as the water of the calorimeters in order that equilibrium in the circulation should be attained. Then while sitting comfortably he held his hands in the calorimeters for from 10 to 30 minutes;

¹ STEWART: *Heart*, 1911, iii, p. 33.

² HEWLETT: *Heart*, 1910, ii, p. 230.

the water was stirred almost constantly and the temperature read at intervals of two minutes.

While our data have been obtained from six men, three (Havens, Schneider, and Sisco) were studied more thoroughly at both altitudes than the others. In each of the six subjects the amount of the blood flow through 100 c.c. of hand volume was greater on the summit of Pike's Peak than in Colorado Springs. Table I contains these data. Since there are individual differences requiring explanation each subject will be discussed separately.

For Havens the average increase in the blood flow on Pike's Peak was for the right hand 65 and the left hand 70 per cent. This subject during the spring months was in training for the two mile run and consequently exercised daily. The determinations in Colorado Springs on March 20, April 1 and 15, were made during the afternoons and were preceded by a morning workout on the track. During the summer and autumn he had taken almost no exercise and spent much of each day in laboratory work. It may be only a coincident and not the result of the physical condition of the subject that his blood flow in the hands averaged in Colorado Springs about 50 per cent less in the autumn when out of training than during the spring months of vigorous exercise. His average amount of blood flow in Colorado Springs during the spring months was 8.6 grams per minute in 100 c.c. of hand and for the fall 4.2 grams. A further point indicating the value of physical fitness is found in the smaller increase in the blood flow during the expedition to the summit in May. At that time the percentage increase was for the right hand 24 and the left hand 29, much below the average of increase for the two expeditions. It should be borne in mind that he walked up the mountain in October and this may account for the constantly higher rate of flow during the autumn expedition.

The variations in Havens' records while on Pike's Peak may be explained in part. The high rates of June 1, October 23 and 25, were associated with an accelerated pulse rate and on each occasion the pulse pressure was 36 mm., which was a little above his average of 33 mm.

Schneider had about the same rate of blood flow during both sojourns on the summit with an average increase of 76 per cent

| | 2 | " | " | 83 | 38.00 | 21.1 | 42.3 | 395 | 41.5 | 40.7 | 9.8 | 10.3 |
|---------|---|---|---|-----|-------|------|------|-----|------|------|-------------|-------------|
| Oct. 23 | | " | " | 100 | 37.33 | 16.0 | 42.3 | 412 | 52.3 | 46.6 | 12.4 | 11.3 |
| 25 | | " | " | 92 | 37.44 | 19.0 | 419 | 434 | 49.8 | 51.1 | 11.8 | 11.5 |
| | | | | | | | | | | | 11.2 | 11.2 |

| SCHNEIDER | | | | | | | | | | | | |
|-----------|--|---------------|------------|-----|-------|------|-----|-----|------|------|-------------|------------|
| Mar. 20 | | Colo. Springs | 4.30 P.M. | 76 | 37.56 | 19.1 | 396 | 401 | 23.2 | 27.4 | 5.9 | 6.8 |
| Apr. 1 | | " | 11.20 A.M. | 76 | 37.22 | 21.4 | 430 | — | 22.8 | — | 5.3 | — |
| 15 | | " | 10.55 " | 84 | 37.67 | 20.5 | 388 | 374 | 26.7 | 24.4 | 6.9 | 6.6 |
| May 13 | | " | 2.30 P.M. | 82 | 37.56 | 21.8 | 398 | 388 | 21.1 | 23.8 | 5.3 | 6.1 |
| Nov. 14 | | " | 9.00 " | 80 | 37.11 | 21.0 | 420 | 395 | 41.3 | 31.6 | 9.5 | 7.3 |
| Nov. 20 | | " | 11.30 A.M. | 72 | 36.84 | 20.0 | 409 | 398 | 16.3 | 16.4 | 3.8 | 4.1 |
| Dec. 18 | | " | 3.20 P.M. | 84 | 37.17 | 20.4 | 403 | — | 18.3 | — | 4.5 | — |
| | | | | | | | | | | | 5.9 | 6.2 |
| May 29 | | Pike's Peak | 8.30 P.M. | 90 | 36.62 | 23.8 | 405 | 388 | 39.3 | 33.1 | 9.7 | 8.5 |
| 30 | | " | 2.25 " | 100 | 37.56 | 20.5 | 398 | 383 | 43.1 | 43.4 | 10.8 | 11.3 |
| June 1 | | " | 12.05 " | 92 | 37.33 | 20.6 | 404 | 395 | 35.0 | 34.8 | 8.7 | 8.8 |
| 2 | | " | 11.40 A.M. | 94 | 37.56 | 20.6 | 405 | 402 | 47.7 | 38.6 | 11.8 | 9.6 |
| Oct. 24 | | " | 12.30 P.M. | 102 | 37.44 | 21.0 | 404 | 398 | 41.6 | 40.0 | 10.3 | 10.0 |
| 25 | | " | 7.15 " | 92 | 37.22 | 20.0 | 424 | 407 | 46.3 | 35.3 | 11.0 | 8.7 |
| | | | | | | | | | | | 10.4 | 9.6 |

| EAGER | | | | | | | | | | | |
|---------|---------------|------------|-----|-------|------|-----|-----|------|------|-------------|-------------|
| Oct. 3 | Colo. Springs | 3.00 P.M. | 76 | 36.50 | 19.6 | 450 | 440 | 18.0 | 17.5 | 4.0 | 3.9 |
| Nov. 20 | " | 10.00 A.M. | 80 | 37.00 | 21.5 | 395 | 427 | 29.7 | 29.9 | 7.5 | 7.0 |
| 26 | " | 3.30 P.M. | 89 | 37.44 | 19.5 | 405 | 388 | 23.6 | 19.1 | 5.8 | 4.9 |
| Oct. 25 | Pike's Peak | 10.30 A.M. | 106 | 36.94 | 20.2 | 395 | 396 | 35.4 | 33.2 | 5.8 | 5.3 |
| MUNRO | | | | | | | | | | | |
| Oct. 3 | Colo. Springs | 5.00 P.M. | 68 | 37.84 | 19.9 | 444 | 409 | 22.7 | 18.9 | 5.1 | 4.6 |
| 10 | " | 3.00 " | 70 | 37.22 | 22.0 | 444 | 430 | 32.2 | 29.0 | 7.3 | 6.7 |
| Nov. 14 | " | 7.00 " | 74 | 37.44 | 20.9 | 460 | 449 | 35.1 | 34.1 | 7.6 | 7.1 |
| Oct. 24 | Pike's Peak | 12.10 P.M. | 96 | 37.39 | 20.6 | 446 | 436 | 33.0 | 29.7 | 7.4 | 6.8 |
| 25 | " | 9.00 A.M. | 96 | 36.84 | 18.6 | 462 | 427 | 46.0 | 40.0 | 10.0 | 9.4 |
| | | | | | | | | | | 8.7 | 8.1 |
| ROBISON | | | | | | | | | | | |
| May 1 | Colo. Springs | 9.05 A.M. | 70 | 37.12 | 21.9 | 448 | 437 | 38.9 | 37.0 | 8.7 | 8.5 |
| May 31 | Pike's Peak | 9.25 A.M. | 90 | 37.61 | 18.3 | 417 | 400 | 49.8 | 49.4 | 11.9 | 12.4 |
| June 1 | " | 7.40 " | 85 | 37.25 | 20.6 | 418 | 395 | 55.1 | 50.4 | 13.2 | 12.8 |
| | | | | | | | | | | 12.6 | 12.6 |

for the right hand and 53 per cent for the left hand. The higher rate in him was undoubtedly largely due to the increase in heart rate, the pulse pressure averaged 34 mm. at both altitudes. The determination on May 30 occurred during an attack of mountain sickness while arterial pressures were extraordinarily high, systolic 138 mm. and pulse pressure 44 mm. At that time the venous pressure also reached a maximum of 20.6 cm. of water.

A greater fluctuation occurred in the blood flow of Sisco while on Pike's Peak than in any other of our subjects. His pulse rate was also more changeable on the summit than in Colorado Springs. The first determination made on him twenty-four hours after the ascent in May showed no increase whatever. At that time his pulse rate was greater than it generally was in the blood flow studies in Colorado Springs. However, his systolic pressure was only 110 mm., the lowest found in him, and the pulse pressure was also unusually low, only 26 mm.; his average being 32 mm. The blood flow per 100 c.c. of hand volume was almost 100 per cent greater the following day, May 31, with the pulse rate practically the same. There was, however, a slight rise in arterial pressure, the systolic pressure was 114 mm. and the pulse pressure 31 mm. The maximum flow, on June 1, occurred at a time when the systolic pressure was 120 mm., the highest obtained on him on the Peak; but the pulse pressure, 34 mm., was not equally raised. With these changes was associated a moderate acceleration of the heart rate. Sisco showed at the high altitude an average increase of 58 per cent for the right and 66 per cent for the left hand.

Our study of Eager and Munro was unfortunately brought to a sudden end on the Peak by the breaking of the glass flasks used for measuring the water for the calorimeters. Two determinations were made on Munro and only one on Eager. The first on Munro, like the first for Sisco, gave no change; the second, however, gave an increase over the Colorado Springs rate of 54 per cent for the right and 49 per cent for the left hand. His average percentage increase for the two determinations was right 30 and left 33. The determination of blood flow for Eager made two days after the ascent showed an acceleration of 55 per cent for the right and 58 per cent for the left hand.

The observations on Robison, while too few to be wholly satisfactory, are of more than passing interest because he had resided for more than four weeks on the summit at the time his circulation rate was determined. It is interesting, therefore, to find that he too had an augmented flow; 45 for the right and 48 per cent for the left hand. This is somewhat less than that found for other subjects. His pulse rate was 20 and 15 beats more rapid than during the experiment in Colorado Springs. The differences in the arterial pressures are of interest, on May 1 while in Colorado Springs the systolic was 114 mm. and the pulse pressure 30 mm.; during both observations of the blood flow on the summit the systolic was 110 mm. and the pulse pressure only 26 mm. If the pulse rate be multiplied by the pulse pressure and the product be taken as a measure of the volume per minute of the blood stream, it will be found that the increase on May 31 should have been only 18 per cent and on June 1 12 per cent. This fact suggests the occurrence of vasomotor changes that our methods have failed to detect.

The augmentation in blood flow found to occur in all of our subjects on Pike's Peak is greater than in other oxygen-want adaptive changes. It should here be noted that in calculating the data for the blood flow we have not corrected the specific heat of the blood constant for the increase in red corpuscles on Pike's Peak. This correction has been neglected because the number of corpuscles was constantly increasing and further it would only add slightly to the figures recorded for the flow. That the average flow would decrease somewhat with longer residence on the Peak is suggested by the observations on Robison and by the experience of the English-American Pike's Peak Expedition¹ in which they found the pulse rate to be slightly reduced from the maximum after a residence of two weeks.

On considering all of our data we are forced to conclude that the facts of the blood pressures and changes in pulse rates do not wholly account for the augmentation in the blood flow observed at the high altitude. There were vasomotor changes for which we cannot account. It was our experience during both expedi-

¹ DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *Philosophical Transactions of the Royal Society of London*, 1913, Series B, ciii, p. 270.

tions that each of us was more sensitive to heat on the mountain than we were at 6000 feet and that we felt comfortable at a lower room temperature. On looking over the room temperatures experienced during the experiments on Havens, Schneider, and Sisco we fail to find here an explanation of the variations. For none of these three men was the most rapid flow coincident with the highest room temperature. The slowest rate for Sisco was associated with the minimum room temperature; but this was not the case for the others. It appears, therefore, that room temperature does not explain the vasomotor changes.

That the body temperature was not instrumental in altering the vasomotor relations is also evident when the more extended records of Havens, Schneider, and Sisco are examined. Havens had one of the lower rates of blood flow on the day his body temperature was the highest, 38° C. For Schneider the more rapid rates occurred when body temperature was the highest, but the small increase in temperature of 0.23 of a degree would very likely be ineffective as a stimulating factor. With Sisco the maximum rate occurred on a day when his body temperature was also maximum, but the next day while the body temperature was still the same the rate of blood flow had lowered 37 per cent.

It is now generally recognized that the rate of flow of the blood from arteries to veins does not depend upon the arterial pressure alone but that two other factors, the caliber of the vessels between artery and vein, and the venous pressure, are of prime importance. We have shown in our former paper¹ that the venous pressure of all our subjects, with the exception of Schneider, was decidedly lowered — 25 to 87 per cent — on Pike's Peak. The fall in venous pressure along with the acceleration of pulse rate will in large part account for the observed increase in the rate of blood flow at the high altitude. However, there are some irregularities involving an increase in the caliber of the arterioles for which we do not account.

It would be interesting for such a study as ours to have a subject who reacted as did Haldane,² whose pulse rate was from 15 to 20 beats slower on Pike's Peak than at sea-level. From a

¹ SCHNEIDER and SISCO: *loc. cit.*

² DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *loc. cit.*, p. 265.

study of his pulse rate and amplitude of heart beat it was concluded that his circulation rate was decidedly decreased at the high altitude. Very likely his venous pressure lowered with residence on Pike's Peak but it is unlikely that the circulation rate was unaltered and certainly it appears that it could not have been accelerated.

THE INFLUENCE OF OXYGEN INHALATION ON THE HEART RATE

If it is the oxygen-want at low barometric pressures that is responsible for the accelerated heart action and the observed increase in the rate of the flow of blood through the tissues, it is probable that inhalation of oxygen may so benefit the body that the heart rate will be retarded and the blood flow diminished. We have tested the influence of oxygen inhalation on both the pulse rate and blood flow.

One of us¹ reported from a series of studies on Mr. Robison, the resident manager of the Summit House on Pike's Peak, that the breathing of oxygen-rich mixtures caused in him, when on the summit, a marked slowing of the pulse rate. It was suggested that the effect of the oxygen was exerted through the oxidation of certain easily oxidizable metabolites normally present in a considerable amount in the blood at very high altitudes. It was also pointed out that these readily oxidizable metabolites accumulate in the blood because of the deficient supply of oxygen and that they may in turn accelerate the heart rate.

We have now compared the influence of oxygen on the pulse rate in Colorado Springs and on Pike's Peak on six subjects and have found the slowing action in each to be more pronounced on the Peak. For this study the subject sat quietly for ten or more minutes, or until the heart rate became constant. The oxygen was then administered by means of a small closed apparatus provided with a soda-lime chamber, for the absorption of carbon dioxide, and with a rubber balloon for the reception of the tidal air and the reserve supply of oxygen. The oxygen was introduced continuously at a uniform rate which was determined by the need of the subject. The oxygen was pure, made from ozone. All

¹ SCHNEIDER: This journal, 1913, xxxii, p. 300.

air was thoroughly washed out of the apparatus with the oxygen before each experiment. The mouthpiece and all tubes were of a large size so that the resistance was reduced to a minimum and the breathing was comfortable. The oxygen was generally administered for ten minutes. The pulse was counted every minute during oxygen inhalation and for an equal interval on return to air. The results of the experiments are given in Table II.

It will be seen that the amount of slowing in Colorado Springs varied from 2.5 to 8.8 per cent. The extent of slowing was not determined by the heart rate at the time the oxygen was administered; thus in the case of Havens in one experiment with a cardiac rate of 80 a reduction to 78 or only 2.5 per cent occurred, while at another time with an initial rate of 62 the heart responded with a slowing of 4.8 per cent. Individual differences appear among the records in Colorado Springs, thus the retarding effect of the oxygen was less pronounced for Havens than for Sisco, Robison, or Munro. The average reduction obtained for the six subjects in Colorado Springs was 5.4 per cent.

Many oxygen breathing tests have been made with men in Colorado Springs and all, with one exception, have responded with a definite, though usually slight, slowing of the heart. The exception was Robison immediately after his descent from the Peak in November, 1912; the case has been discussed by Schneider.¹ At that time the partial pressure of oxygen in Robison's blood was extraordinarily high because he continued for a time to ventilate his lungs as thoroughly as on the Peak and this resulted in an alveolar oxygen pressure at least 10 mm. above that found in men acclimatized to the altitude of Colorado Springs.

On Pike's Peak we were able to reduce the pulse rate in our six subjects from 7.4 to 20.8 per cent. The least reduction, that of 7.4 per cent, occurred in Havens at a time when his heart rate had not taken up the high tempo of the later days. It will be recalled that his pulse rate did not clearly accelerate on the Peak for forty-eight hours. All other tests with oxygen on the mountain show a retardation of 10 or more per cent. The average amount of slowing for all our subjects while on the Peak was 14 per cent.

Since the cardiac rate may be so decidedly slowed at an

¹ SCHNEIDER: *loc. cit.*

TABLE II
SLOWING THE HEART WITH OXYGEN

| Subject | Date | Place | Pulse rate with air | Pulse rate with O ₂ | Percent. of slowing |
|-----------|---------------|---------------|------------------------|-----------------------------------|------------------------|
| Havens | Apr. 17, 1913 | Colo. Springs | 62 | 59 | 4.8 |
| " | May 8 | " " | 68 | 64 | 5.9 |
| " | 21 | " " | 70 | 67 | 4.3 |
| " | Nov. 19 | " " | 80 | 78 | 2.5 |
| " | May 30 | Pike's Peak | 68 | 63 | 7.4 |
| " | 31 | " " | 79 | 70 | 13.0 |
| " | Oct. 25 | " " | 92 | 82 | 10.9 |
| Schneider | May 21 | Colo. Springs | 76 | 74 | 2.6 |
| " | Nov. 14 | " " | 80 | 75 | 6.3 |
| " | Dec. 18 | " " | 82 | 78 | 4.9 |
| " | May 30 | Pike's Peak | 90 | 79 | 12.2 |
| " | 31 | " " | 92 | 80 | 13.0 |
| " | Oct. 24 | " " | 108 | 96 | 11.1 |
| " | 25 | " " | 102 | 88 | 13.7 |
| Sisco | May 8 | Colo. Springs | 64 | 59 | 7.8 |
| " | 21 | " " | 62 | 59 | 4.8 |
| " | Nov. 19 | " " | 72 | 67 | 6.9 |
| " | May 30 | Pike's Peak | 72 | 62 | 13.9 |
| " | 31 | " " | 70 | 63 | 10.0 |
| " | Oct. 24 | " " | 88 | 78 | 11.4 |
| Robinson | Oct. 13, 1912 | " " | 80 | 64 | 20.0 |
| " | 14 | " " | 82 | 70 | 14.6 |
| " | May 30, 1913 | " " | 88 | 70 | 20.4 |
| " | 1 | Colo. Springs | 68 | 62 | 8.8 |
| Munro | Oct. 24 | Pike's Peak | 96 | 76 | 20.8 |
| " | Nov. 14 | Colo. Springs | 72 | 66 | 8.3 |
| Eager | Oct. 24 | Pike's Peak | 106 | 88 | 17.0 |
| " | Nov. 14 | Colo. Springs | 88 | 84 | 4.5 |
| " | Dec. 18 | " " | 90 | 87 | 3.3 |

altitude of 14,109 feet by the breathing of oxygen-rich mixtures, the conclusion follows that the quickened action of the heart in rarefied air is a means of compensating for the lack of oxygen.

Arterial pressures were determined in some of the oxygen inhalation experiments, both in Colorado Springs and on Pike's Peak, but no definite evidence of change was obtained. Unfortunately no determinations of venous pressure under these conditions have as yet been made.

THE INFLUENCE OF OXYGEN INHALATION ON THE BLOOD FLOW

We have made a partial study of the influence of the inhalation of oxygen on the blood flow in the hands. Unfortunately this work was interrupted when we were last on Pike's Peak by an accident to our apparatus. Consequently certain control tests we had planned have had to be omitted. However, since the data obtained are on the whole concordant we venture to make a tentative report at this time.

The normal rate of the blood flow was determined for ten or more minutes, this was followed by another period of at least ten minutes during which the subject breathed oxygen through the apparatus used in slowing the heart rate, and then occurred an after air period of the same length of time. In six out of seven experiments on the Peak there was a diminution in the rate of the blood flow during the oxygen inhalation period. Two protocols giving calorimeter readings and pulse rates are cited to show the sequence of the changes.

EAGER. Mouth temperature, 36.56° . Rectal temperature, 36.94° .

Volume of the hand 396 c.c. Hand put into the calorimeter containing 3015 c.c. of water at 10.46 a.m. Following Stewart's suggestion for computation we find that during the first air breathing period of ten minutes there was a flow of 33.2 gm. per minute for the entire hand and 9 gm. per 100 c.c. of hand per minute. In the oxygen breathing period there were 27.5 gm. for the hand and 7 gm. for 100 c.c. of hand volume. During the after period these were 36.1 and 9.1 gm. each.

SISCO. Mouth temperature, 36.61° . Rectal temperature, 37° . Volume of the hand 430 c.c. Hand put into the calorimeter containing 3015 c.c. of water at 9.34 a.m. During the first period the flow

for the entire hand was 44.1 gm. of blood per minute or 10.3 gm. per 100 c.c. of hand per minute. For the oxygen inhalation period the flow for the whole hand was 39.9 gm. and 9.3 gm. for 100 c.c. of hand per minute. In the after period these figures are 45.0 gm. and 10.7 gm. respectively.

EAGER

SISCO

| Time | Calori- meter | Pulse Rate | Notes | Time | Calori- meter | Pulse Rate | Notes |
|-------|------------------|---------------|---------------|-------|------------------|---------------|---------------|
| 10.50 | 31.49 | 106 | Air breathing | 9.38 | 29.78 | 88 | Air breathing |
| 10.52 | 31.52 | ? | Room 20.1 | 9.40 | 29.91 | | Room 21.4 |
| 10.54 | 31.63 | 105 | | 9.42 | 30.04 | | |
| 10.56 | 31.69 | | | 9.44 | 30.17 | | |
| 10.58 | 31.73 | 106 | | 9.46 | 30.26 | 88 | Room 21.4 |
| 11.00 | 31.79 | | Oxygen on | 9.48 | 30.41 | | Oxygen on |
| 11.02 | 31.81 | 92 | | 9.50 | 30.48 | 80 | |
| 11.04 | 31.89 | 88 | Room 20.1 | 9.52 | 30.54 | 76 | |
| 11.06 | 31.93 | 88 | | 9.54 | 30.66 | 78 | |
| 11.08 | 31.98 | 84 | | 9.56 | 30.81 | 78 | Room 21.6 |
| 11.10 | 32.00 | 88 | Oxygen off | 9.58 | 30.91 | 78 | Oxygen off |
| 11.12 | 32.05 | 90 | | 10.00 | 31.03 | 84 | |
| 11.14 | 32.11 | | | 10.02 | 31.12 | 88 | Room 20.9 |
| 11.16 | 32.18 | 106 | | 10.04 | 31.28 | | |
| 11.18 | 32.22 | | Room 20.2 | 10.06 | 31.39 | | |
| 11.20 | 32.29 | | | 10.08 | 31.44 | | Hand out |
| 11.22 | 32.33 | | Hand out | 10.18 | 31.33 | | Room 20.5 |
| 11.32 | 32.21 | | | | | | |

It should be noted that the diminution in the flow of the blood in the hands during oxygen inhalation was immediate and was in general, as for Sisco, most marked the earlier minutes of the period. The slowing of the heart ordinarily took place more

gradually and did not tend to return to the normal rate as did the flow of the blood in several instances.

TABLE III

BLOOD FLOW IN 100 C.C. OF HAND DURING OXYGEN INHALATION ON PIKE'S PEAK

| Subject | Date | Blood flow in grams per Minute | | | Slowed with O ₂ % | Heart slowed with O ₂ % |
|-----------|---------|--------------------------------|---------------|--------------|---------------------------------|---------------------------------------|
| | | Fore-period | Oxygen-period | After-period | | |
| Eager | Oct. 24 | 8.4 | 7.0 | 9.1 | 16.7 | 17.0 |
| Havens | 24 | 11.8 | 9.5 | 13.5 | 19.5 | 10.9 |
| Munro | 24 | 7.4 | 7.0 | 7.0 | 5.7 | 20.8 |
| " | 25 | 10.0 | 9.1 | 10.0 | 9.0 | — |
| Schneider | 24 | 10.3 | 9.9 | 10.5 | 3.9 | 11.1 |
| " | 25 | 11.0 | 10.9 | 11.9 | 0.9 | 13.7 |
| Sisco | 24 | 10.3 | 9.3 | 10.7 | 9.7 | 11.4 |

A summary of all the observations on the influence of oxygen on the blood flow made on Pike's Peak is given in Table III. The retardation in the flow in the six positive experiments ranged from 3.9 to 19.5 per cent. The diminution in the rate of flow was not parallel with that of the pulse rate. Generally the percentage decrease in the blood flow was less than that of the pulse rate. In Havens, however, the flow of blood was reduced 19.5 per cent while his heart rate decreased only 10.9 per cent. A satisfactory explanation of these differences is not at hand. In our records of the heart slowing we find that for each subject, except Havens, the pulse became fainter and usually felt softer during oxygen inhalation, while on the contrary Havens' pulse became harder and more pronounced. The change in the character of the pulse, in all cases except Havens, suggests a decrease in the heart amplitude as an explanation of the diminished blood flow. Attention is called to the fact that in five out of the seven experiments there was a greater flow in the after-period than in

the fore-period. A detailed study of these various irregularities will be made in a future expedition to Pike's Peak.

In Colorado Springs experiments made on five of our subjects have failed to show a slowing of the blood stream when the subject was in a normal condition. Thus in one series of oxygen inhalation experiments we obtained the following rates per minute:—Eager, fore-period 7.5 gm., oxygen-period 8.4 gm.; Havens, fore 4.9 gm., oxygen 4.8 gm.; Munro, fore 7.7 gm., oxygen 7.8 gm.; Schneider, fore 4.5 gm., oxygen 5.1 gm.; and Sisco, fore 5.9 gm., and oxygen 6.5 gm. We have, however, two experiments made in Colorado Springs in which a diminution in the flow occurred during oxygen inhalation. One of these was with Eager one hour after he had pushed a heavy motorcycle several miles on a dusty road, then the rate of blood flow per minute in 100 c.c. of hand was in the fore-period 10.1 gm., during the oxygen inhalation-period 8.1 gm., and in the after-period 9.4 gm. The second experiment was with Schneider at the end of a very busy day. Then the blood flow in his hands averaged 8.4 gm. in the fore-period, 7.6 gm. in the oxygen-period, and 8.1 gm. during the after-period.

The influence of oxygen on the rate of the blood flow at the high altitudes is the opposite of that shown by Stewart¹ in a case of cyanosis in which inhalation of oxygen increased the flow of the blood by an amount varying from 30 to 70 per cent. It should here be noted that Stewart found the breathing of oxygen did not change the rate of the blood flow in the hands of two normal men at a low altitude. Our results in part resemble those obtained by Stewart² on two healthy men during forced breathing. A distinct diminution in the flow through the hands was observed by him during the periods of increased respiration. We have tried to avoid forced breathing in our experiments. Since the conditions of experimentation were the same in Colorado Springs and on Pike's Peak, and at the lower altitude ordinarily no change occurred, we believe that forced breathing may be eliminated as an explanation of our results. A difference in the reaction will

¹ STEWART: *Journal of pharmacology and experimental therapeutics*, 1911, ii, p. 477.

² STEWART: *This journal*, 1911, xxviii, p. 190.

be observed on comparing Stewart's and our data. In forced breathing the change in blood flow required some minutes to reach its maximum while with our oxygen experiments it was almost immediately maximal. We also found that the heart rate increased during the forced breathing while in our experiments with oxygen inhalation the rate decreased.

The above experiments dealing with the effects of oxygen inhalation on the heart rate and the velocity of blood flow indicate that it is the lack of oxygen at high altitudes that calls forth the changes within the circulatory system. Alterations in the composition of the blood very likely influence the heart and the vasomotor mechanism. Durig and Kolmer¹ after finding the heart rate to be permanently augmented by residence on Monte Rosa question as to the causes of acceleration. It will be recalled that they found the heart rate accelerated for two or three days following ascent; after which there was some retardation, but never a return to the rate generally found at low altitudes. They associated the early augmentation in part with an increased body temperature, and in part with the altered composition of the blood resulting from the lack of oxygen. They assumed that the retardation was caused by an increased tone of the cardio-inhibitory center and that this heightened tone was associated with the more intense stimulation of the lung fibers of the vagus nerve in consequence of increased lung ventilation. We as yet are not prepared to debate the questions as to the cause or causes of the acceleration or how the stimulus acts. A study of these questions is in progress and the investigation will be continued in another and longer expedition to Pike's Peak. It here should be noted, however, that our temperature records (see table on the blood flow) fail to support Durig and Kolmer's contention that a rise in the body temperature causes, in part or wholly, the initial augmentation in heart rate. Our men did not have a higher temperature on Pike's Peak than in Colorado Springs.

Attention is called to the fact that with oxygen we slowed the heart of Robison, whom we take it was fully acclimatized to the

¹ DURIG: *Physiologische Ergebnisse der im Jahre 1906 durchgeführten Monte Rosa-Expedition*, p. 48.

altitude of 14,109 feet, as much as in any, and more than in the majority, of the members of our expeditions. Unfortunately we did not test the influence of oxygen on the rate of blood flow with Robison.

SUMMARY

1. The rate of blood flow in the hands of the six men examined was increased by residence on Pike's Peak by an amount varying from 30 to 76 per cent. The increase in the rate of flow has been associated in part with an augmented rate of heart beat and a fall in the venous pressure, also in part with a dilatation of the arterioles.

2. The breathing of an oxygen-rich mixture slowed the heart rate in each of the six subjects to a greater degree on Pike's Peak than in Colorado Springs. The average retardation was 14 per cent at 14,109 feet, and 5.4 per cent at 6000 feet.

3. The arterial pressure was not clearly altered at either altitude during oxygen inhalation; but the pulse, with one exception, was fainter and softer.

4. Oxygen inhalation diminished the rate of blood flow in the hands from 4 to 20 per cent on Pike's Peak while the flow was not ordinarily altered in Colorado Springs.

5. In view of the beneficial influence of oxygen inhalation — the retardation of the heart rate and diminution in the rate of blood flow — it was concluded that oxygen-want induces the adaptive high altitude circulatory changes.

A STUDY OF THE MECHANISMS BY WHICH MUSCULAR EXERCISE PRODUCES ACCELERATION OF THE HEART

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THE mechanisms which have been described as concerned in acceleration of the heart during exercise may be divided into two classes: first, those depending on the physical and chemical changes in the blood, and, second, those depending on nervous impulses of either central or peripheral origin. Most work on the subject has favored the latter class of mechanisms. Petersen and Gasser¹ have recently found that the rate of excised hearts is not increased by extracts of fatigued muscles although the amplitude may become greater, while Athanasius and Carvallo² long ago showed that acceleration might be purely nervous in origin. This was done by binding the arm with an Esmarch bandage. On working a dynamometer with the hand thus rendered anaemic the heart accelerated from 10 to 20 beats per minute. These authors felt that if the chemical products of muscular contraction affected the heart it was only after prolonged exercise and the action was more nearly pathological than physiological.

That the acceleration in exercise is not due to chemical or physical changes in the blood but rather to nervous phenomena of some kind is also indicated by the interesting observations of Bowen³ and Buchanan.⁴ Bowen studied the latent period of the acceleration following the onset of exercise. He determined by continuous graphic records of the pulse that the diastole of the next pulse cycle occurring after the commencement of exercise is materially shortened, and he therefore gave the latent period as one cardiac cycle. Buchanan, by measuring the length of the heart cycle with the capillary electrometer, also found that the acceleration occurs so promptly that even if the muscular contraction takes place at the end of a systole the immediately en-

suing diastole of the same cycle is shortened. In one case the cycle was shortened to 81 per cent of the preceding. We have confirmed these results by electro-cardiographic methods. The duration of the pulse cycle was obtained with great accuracy on a rapidly moving photographic registration apparatus, and the exercise, which consisted in clenching the fist, was simultaneously recorded by a tambour connected with an aspirator bulb held in the hand clenched. One of our records shows that the first cycle following the clenching of the fist was shortened 9 per cent and the second 25 per cent. It took exactly 1.09 seconds for this 25 per cent increase in rate to be brought about.

Inasmuch as the latent period for the acceleration of the heart has been proved to be one cardiac cycle or less, the possibility is at once eliminated that chemical products of muscular metabolism or the heat evolved in such metabolism could have had time to reach the heart. The first acceleration in exercise can therefore scarcely be due to any direct action of metabolites on the heart or cardiac centres, or to a reflex arising from stimulation of sensory nerves in the heart by heat, as is maintained by Mansfield,⁵ or to inhibition of the vagal centre by afferent impulses from the lungs arising from increased respiration, as is maintained by Hering.⁶ Apparently the only mechanism in the body that could act within the specified time limits is one that is purely nervous in character.

The results just detailed give considerable support to Johansson's⁷ theory that impulses along the motor paths affect the cardiac centres of the medulla. This author found that tetanization of the hind limbs by stimulation of the severed spinal cord produced a cardiac acceleration that was very small compared with that occurring in normal voluntary movement. He attributed this difference to a psychic stimulation of the accelerator centre occurring during the voluntary activity, strengthening his conclusions by the observation that passive movements of the limbs in the normal animal produce very little acceleration. Johansson gave no reason for his assumption that the nervous action was on the accelerator centre rather than on the cardio-inhibitory.

Athanasius and Carvallo² advanced an entirely different expla-

nation for acceleration in exercise which was based on the following observations: First, that when paraplegic individuals were ordered to make voluntary efforts to move their disabled limbs no acceleration resulted. Second, that on mechanically exciting an animal poisoned with chloralose the resulting muscular activity produced an increased heart rate, but if no movements resulted the acceleration was absent. They concluded from these by no means conclusive experiments that the voluntary motor impulse is alone insufficient to cause an acceleration of the heart and that reflex movements very efficiently produce it. In this way they came to the view that the working muscles send excitations toward the higher centres, which in their passage through the medulla depress the cardio-inhibitory centre. Athanasia and Carvalho based their conclusion that it is the cardio-inhibitory centre that is concerned upon some experiments on animals a few hours after vagotomy. Pulling rhythmically on the hind limbs caused the animals to withdraw them actively, but the movements now produced no acceleration, although the same manipulation did increase the heart rate of the normal animal.

Hering⁶ studied the role of the extrinsic cardiac nerves in motor accelerations of the heart by determining the heart rate as the result of exercise before and after removal of the stellate ganglia. He found that after removal of these ganglia the rate following exercise was considerably less than normal, while the resting rate was considerably higher. The acceleration was, therefore, much reduced. As a result he arrived at the conclusion that the increase in heart rate in muscular activity is principally dependent on the integrity of the accelerator nerves. This he believed to be supplemented especially in the early stages of exercise by diminution of vagal tone, but only in so far as this is brought about by the increased respiratory rate resulting from the increased muscular activity.

The mechanism of reflex cardiac acceleration due to stimulation of sensory nerves has been investigated by several workers and the results have been rather freely applied in explaining increased heart rate during exercise. MacWilliam⁸ came to the conclusion that reflex acceleration is dependent on depression of the vagus centre, since it occurs with remarkable suddenness, rises rapidly

to its maximum, remains essentially the same after section of the accelerators, and since direct stimulation of the accelerators is followed by an increase in rhythm only after a long latent period. A number of years later this same field was covered independently by Hunt,⁹ whose work confirmed that of MacWilliam's. Hunt showed that in reflex acceleration the response is the same as that occurring on cutting the vagi; that is, the diastole is markedly shortened. This is in marked contrast to the results obtained by accelerator stimulation, in which case both systole and diastole were shortened.

Aulo¹⁰ suggested that by Hunt's criterion for depression of the cardio-inhibitory centre the nature of acceleration in exercise might be determined from the sphygmogram. Curves were therefore taken and it was shown that in exercise for periods of one minute, at least, the diastole was the part shortened. Aulo from these observations concluded that if Hunt's criterion is correct the first increase in pulse rate results from a diminution of vagal tone.

In the light of our present knowledge it seems that acceleration of the heart in exercise is best attributed to nervous mechanisms. Although experimentally it is clear that reflex acceleration may be produced either by depression of vagal tone or stimulation of the accelerators,²⁰ workers are not yet agreed as to which of the two centres is normally more affected, no matter whether the stimulus should prove to be an irradiation from voluntary impulses, or a sensory one from peripheral parts.

Our own work was taken up primarily to determine the relative parts played by the vagi and accelerators in cardiac accelerations during the early stages of exercise. The investigation has been carried out according to the following scheme. Accelerations occurring in exercise were determined: (1) When both the accelerator and inhibitory mechanisms were intact; (2) when the accelerator mechanism was eliminated and the inhibitory mechanism was intact; (3) when the inhibitory mechanism was eliminated and the accelerator intact; and (4) when the heart was freed from all extrinsic nervous control. An inquiry was also made in regard to factors causing accelerations after all the extrinsic nerves had been eliminated.

METHODS

The experiments were performed entirely on dogs. It was first necessary to get the pulse of the normal dog at rest. To do this the dog was made to lie quiet until the pulse rate no longer decreased. The rectal temperature was then taken. The dog was exercised for two minutes, the exercise consisting in making the dog run as fast as possible at the end of a leash. The pulse was counted immediately at the end of exercise, the loss of time being only a few seconds, and the counting was continued in most cases until the rate returned to normal. The temperature of the animal was again observed. After the temperature returned to normal, atropine was administered subcutaneously to determine the power of the heart to accelerate after complete removal of vagal inhibition. To insure a complete block of the vagal endings 1.5-2 mg. of atropine were administered subcutaneously and after the pulse had reached its maximum an additional half-milligram was given to see if the pulse could be driven any higher. In most cases it was found that after administration of atropine the pulse rate rose rapidly to a maximum, then slightly decreased, remained at this level for a short time and then again gradually decreased. No further injection of atropine could then increase the pulse rate. This decrease in rate must be due to the inability of the heart to maintain such a high frequency, since it has been our experience that several hours after administration of atropine electrical stimulation of the vagus was without effect on the heart. The high pulse rate was readily counted by means of a phonendoscope placed over the chest at the position of the apex beat.

The next step was the removal of the accelerator nerves. The technique may be of use to other workers and will be described in some detail. It will be well to briefly review the anatomy of the ganglion in the dog, especially since it was found to be given incorrectly in some recent textbooks of physiology. As usually seen from the open thoracic cavity it is a white, laterally compressed bean-shaped body shining through the pleura at about the level of the second rib. It lies at the edge of the longus colli muscle with the smallest diameter in the sagittal plane. From

the upper pole, which lies anteriorly and ventrally, the two branches of the ansa subclavia are given off. These pass ventrally one on each side of the subclavian artery to the inferior cervical ganglion. From the anterior portion of the ganglion branches pass to their distribution in the nerves of the brachial plexus. From the dorsal edge arise the rami communicantes to the anterior divisions of the first and second dorsal nerves. The ramus to the third dorsal segment may arise directly from the stellate ganglion, but more often it first joins the sympathetic chain. Posteriorly the ganglion tapers out and is connected with the sympathetic chain at the level of the third rib.

The operations were performed under ether anaesthesia with due aseptic precautions. The incision was made in the midline from the level of the larynx to the suprasternal notch, and the skin separated from the sterno-hyoid and the sterno-thyroid muscles. A separation was made between these two muscles and the carotid sheath exposed. The vagus nerve was then freed from the sheath and its course followed to the inferior cervical ganglion, from which arise the ansa subclavia. The field of operation was most easily exposed by passing the forefinger behind the carotid sheath down into the superior mediastinal space to the level of the third rib. The pleura was carefully lifted from its position over the ganglion. The field was then further exposed by inserting two large flat-bladed retractors into the opening prepared by the finger. With these the subclavian vessels were displaced ventrally and a retractor placed medially served to hold the carotid and vertebral arteries out of the field.

From this time on illumination from a head mirror was necessary. When the ansa subclavia had been found a Halsted mosquito clamp was placed on the dorsal loop and by gentle traction its course was followed to the antero-ventral pole of the ganglion. At this point the rami communicantes to the brachial plexus were encountered. One of the larger of these was secured by a mosquito clamp which was subsequently used as a guide. Both branches of the subclavian loop were then cut, after which each of the branches to the brachial plexus was in turn exposed and severed with a cutting probe. The position of the rami communicantes to the first and second dorsal nerves was de-

terminated and the rami cut. The removal was completed by severing the connection of the ganglion with the sympathetic chain. Care was taken throughout the operation not to produce a pneumothorax by puncturing the pleura, and on the left side the thoracic duct had to be avoided. When its position had been determined it was easily displaced forward with a retractor. The wound was closed by uniting the sterno-hyoid and the sterno-thyroid muscles and then expressing the air from the mediastinum through the suture by pressure on the outside of the thorax. The skin incision was closed by a continuous suture and the neck bandaged without further dressing.

The animals made uneventful recoveries and they were playful and ate well. The only external sign of the removal was the fact that the nictitating membrane extended out over the bulbus oculi, due to its loss of tone after cutting the sympathetic innervation of its retractor muscle. This condition persisted although the membrane later developed a certain amount of tone. The dilation of its vessels which occurred at first usually entirely disappeared.

The completeness of the removal was determined by autopsy in every case. Usually the removal was found to be complete. The ganglion was in most cases found to have been separated from the sympathetic just above the first dorsal ramus. In some cases a tiny speck of the ganglion was found adherent to the third ramus. In some of the earlier operations before the technique was perfected, autopsy showed that the knife had slipped into the ganglion and that portions remained adherent to the second or second and first rami. In no case was there a trace of the antero-ventral half of the ganglion or the cardio-accelerator nerves which arise from it. Data from the earliest experiments in which the autopsy showed incomplete removal of the ganglion were, of course, discarded. In addition to the operations described above several control experiments were made which will be referred to in the text.

After recovery the resting pulse rate of the dog was counted as before and the reaction of the heart to the two-minute period of exercise was determined. The resting pulse was also determined when the vagal endings were blocked by atropine. These obser-

vations were made over periods ranging from sixteen hours to five months after the operation. The vagi were then divided in the neck and similar observations repeated.

I. EFFECTS OF REMOVING THE STELLATE GANGLIA

In six out of nine attempts the autopsies showed that we had succeeded in completely removing the stellate ganglia. Data from the three failures were, of course, rejected. Before the subsequent vagotomies were performed the animals were observed during periods varying from one to nineteen weeks. The principal data will be discussed under the following sections:

1. The resting pulse. — In every case the resting pulse after removal of the accelerators was less than in the normal animal. The pulse rate fell rapidly immediately after the operation and then more gradually decreased until it reached a level at which it remained nearly constant. The immediate decrease in rate was usually over one-half the total. By the end of about the first week following gangliectomy the rate had slowly fallen to a level which was fairly constantly maintained. Apparently the large decrease at first was due to the removal of the tonic accelerator action and the subsequent more gradual decrease was due to the return of the normal tone to the vagi. The decrease from the normal rate differed widely in the different animals, depending mainly on the rate of the normal resting pulse. In dogs 3 and 5, in which the normal resting pulse was high, 140 and 136 per minutes respectively, the corresponding resting pulses after the gangliectomy were 76 and 80, while in dog No. 4 the pulse which was normally 78 fell only to 66. The actual decrease thus varied all the way from 12 to 64 per minute.

So far as the nervous mechanisms are concerned the resting pulse rate might be determined in three different ways, assuming that the inherent automaticity of the heart is fairly constant. Some evidence for such an assumption has been presented by Stewart and Pike,¹¹ who found that the heart rate of cats during cerebral anaemia was remarkably uniform. In the first place the accelerator tone might be a constant factor for the species and the variations in rate be due to vagal activity; in the second

TABLE I

Showing acceleration before and after removal of the stellate ganglia. The resting pulse rates are in each case the lowest found in a series of observations. The accelerations given were observed in the same experiment as that in which the corresponding resting pulse rate was obtained. In experiment No. 5 the rate after removal of the ganglia finally fell to 80 but acceleration was not measured at this time. Rates are given in beats per minute.

| Ex. no. | Before removal | | | After removal | | |
|---------|----------------|--------------|----------|-------------------------|--------------|----------|
| | Pulse at rest | Acceleration | Per cent | Pulse at rest | Acceleration | Per cent |
| 1. | 116 | 44 | 37 | 70 | 42 | 60 |
| 2. | 98 | 50 | 51 | 66 | 48 | 72 |
| 3. | 140 | 44 | 31 | 76 | 50 | 65 |
| 4. | 78 | 52 | 66 | 66 | 36 | 34 |
| 5. | 136 | 38 | 28 | { 96 80 ¹ | 34 — | — — |
| 6. | 88 | 40 | 45 | 72 | 40 | 35 |

¹ The pulse finally fell to 80 in this dog.

place the vagal tone might be constant and variations be brought about by differences in accelerator action; in the third place each of these factors might be variables. Our data seem to enable us to decide between these possibilities.

The normal resting pulse rates of the dogs were respectively 116, 98, 140, 78, 136, and 88 per minute. After the operation the corresponding pulse rates finally fell to 70, 66, 76, 66, 80, and 72. These figures show that after the accelerator action was removed the heart rate became remarkably uniform; the normal pulses differed as much as 62 per minute, while after removal of the accelerators there was a difference of only 14 per minute. If the accelerator action had been a constant and the vagal action variable, then the resting rate after the operation would have varied according to the previous normal resting rates. As this was not the case it is evident that in extirpating the accelerator nerves the variable factor was removed, and the conclusion seems therefore justified that the variations in the resting pulse rates of

our six dogs were in a larger measure dependent on the activity of the accelerators than on any vagal action.

.2. The reaction to muscular exercise.— The ability of the heart to accelerate during muscular exercise after removal of the stellate ganglia was striking. The actual increases in rate per minute before and after the operation were not markedly different. Table I gives the exact figures. If the lowest observed resting rate in each experiment and the corresponding acceleration are compared it will be noted that in one case the acceleration was greater after the operation, in one case the same, and in four cases slightly less. On looking over all observations made it has been found that in the majority of cases the accelerations were a few beats less per minute after removal of the accelerators.

The results obtained show conclusively that the accelerator mechanism is by no means necessary to secure the increase in pulse rate normally occurring at the beginning of ordinary exercise. This conclusion is directly opposite to that reached by Hering.⁶ If we compare our results with his the reason for this becomes at once apparent. In our experiments the resting pulse after the operation was in every case much lower than in the normal animal, and this lower rate was maintained until the death of the animal, one dog being observed for a period of five months. This is what would be expected from our present knowledge of the tonicity of the accelerators. An examination of the pulse rates recorded in Hering's experiments given in Table E, page 469, shows that in every case where the normal resting rate was given it became higher after the operation. In five of the seven experiments it remained higher, and in three cases the rate kept increasing following the recovery of the animal. The motor acceleration following the operation was at first small but it gradually increased.

The possibility was suggested by Hering that in tearing out a part of the sympathetic the function of the remaining portion might be injured, so that in the first exercise experiments the sympathetic accelerator nerves would be partly anatomically and partly physiologically removed from activity. On the return of function to the injured nerves the motor acceleration of the heart would, of course, increase. This possibility he could not

eliminate with certainty. In his method of operation the sympathetic which runs separate from the vagus in the rabbit was followed down to the first thoracic ganglion, which was secured and torn off from the sympathetic chain. The injury was variable in the different cases, in many of which he tore out three ganglia. While post-mortem was made in most cases, he believed the findings were of doubtful value as the field was so scarred over it that it was difficult to find any remaining branches from the sympathetic to the heart.

While Hering's explanation may in a measure be correct it is more probable, inasmuch as the heart was much more rapid after the operation, that the fault lay in an impairment of the vagal action either centrally or peripherally. The latter was probably the reason, because in Hering's description of his operation he says that the nerves which were connected with the ganglion, the depressor and branches of the vagus, were cut across. Furthermore, Friedenthal and Schaternikoff¹² state that in performing this operation a portion of the cardio-inhibitory fibres are always removed.

On the basis of injury to the vagi the failure of Hering's rabbits to accelerate is readily explained. When the heart is not under normal vagus control an increase in rate can hardly be secured by inhibition of the vagal centre. Thus in experiment No. 23 (I) (Table E) where the resting rate was high after the operation and kept on increasing during the succeeding days, the motor acceleration fell far below the normal, and on subsequent section of the vagi the pulse rate fell in spite of the fact that Hering had previously shown that there is considerable vagus tone in the rabbit. On the other hand in experiments No. 12 (II) and No. 14 (II) where the pulse rate fell below the normal resting rate on recovery from the operation, the motor acceleration reached that attained by the intact animal and in No. 14 (II) in which subsequent vagotomy was performed the pulse rate rose following the operation.

A criticism of our results may lie in the possibility of accelerator fibres being present in the vago-sympathetic trunk. However, the improbability of such fibres having any great importance was shown by Hunt. He found that evidence of accelerator

fibres in the vago-sympathetic of the dog occurred only in exceptional cases and when it did occur the acceleration produced was not at all like that obtained reflexly.

The fact that acceleration at the beginning of exercise persists after removal of the accelerators would in itself seem to prove that the increased rate was brought about by means of the inhibitory mechanism. That this is true we have tried to establish in several ways.

As already pointed out the extremely short latent period for exercise acceleration in the normal animal seems explicable to us only on the basis of nervous mechanisms being involved. If this be true, the mere fact that acceleration persists after removal of the stellate ganglia is sufficient proof that the efferent path to the heart is by way of the vagi, provided that the acceleration is of the same type as normally.

If the accelerations during exercise before and after the removal of the stellate ganglia be compared in percentages of the resting rate, it will be found that the acceleration in every case but one is greater after removal of the ganglia. This results from the fact that although the resting rate falls after removal of the accelerators the power to increase the rate a given number of times remains about the same as before. Cardiac acceleration in the normal animal as expressed in percentages is thus largely dependent on the resting rate, or what is the same thing, accelerator tone. In the six intact animals the percentage accelerations for 2 minutes exercise varied from 31 per cent to 66 per cent, averaging 43 per cent. After removal of the accelerators the same amount of exercise produced increases varying from 55 to 72 per cent with an average of 61 per cent. These percentages are of little importance, aside from the fact that they show how little the power of the heart to accelerate in exercise depends on the accelerator mechanism.

Our protocols show that acceleration occurred as quickly after the removal of the accelerators as before. This is in contrast to the results which will be given later of experiments in which the vagi alone were sectioned. Furthermore, the actual acceleration remained approximately the same after the stellate ganglia were removed. These observations seem clearly to indicate that the

same mechanism was active in both cases, that is, the inhibitory mechanism. Bowen³ and Aulo¹⁰ have each shown that acceleration produced by depression of the vagal centre has the same characteristics as that seen in the early stages of exercise. In each the increased rate is brought about by the shortening of the diastole.

By the use of atropine we attempted to determine whether depression of the inhibitory mechanism was alone sufficient to account for the accelerations observed. In dogs Nos. 1, 2, and 3 after 2 mg. of atropine injected subcutaneously the heart rates rose to 232, 230, and 188 per minute respectively. The rates after 2 minutes exercise were 160, 148, and 184. In these same animals after removal of the stellate ganglia 2 mg. of atropine caused the heart to rise to 206, 168, and 200 respectively. The data show that whether the accelerators are intact or not the heart still has a certain power of acceleration which is greater by a large margin than that needed during the early stages of exercise. Diminution of vagal tone can, therefore, readily account for the exercise accelerations.

The question as to whether the inhibitory mechanism was still responsible for the accelerations occurring after extirpation of the accelerators seemed capable of being put to a crucial test by the simple expedient of cutting the vagi. At intervals varying from 1 to 18 weeks after removal of the stellate ganglia the six dogs were therefore vagotomized. The data obtained after this procedure will be presented in the next section.

II. EFFECTS OF VAGOTOMY AFTER PREVIOUS REMOVAL OF THE STELLATE GANGLIA

1. The resting pulse.—After vagotomy in dogs whose accelerators had previously been cut, the pulse rate was greatly increased, its highest point being reached immediately after the operation. Three of the dogs were kept longer than two days after the operation and in these it was noted that the pulse rate fell rapidly from this maximum. Thus in dog No. 6, with a resting pulse of 72 after gangliectomy, the rate went up to 160 immediately after vagotomy. Twenty-four hours following, the

pulse rate was 120, 36 hours following it was 116, at which figure it remained until the end of the third day when the animal was killed.

This fall in rate occurred no matter whether the vagi were cut previous to or subsequent to removal of the accelerators. Thus in dog No. 9, in which the accelerators were intact, immediately after section of the vagi the pulse rate rose to 200 per minute, falling on the second day to 162 per minute, and on the third day to 154 per minute. In both cases this drop in pulse rate was probably due to an impairment of the heart's automaticity by its unrestrained activity.

Our protocols show the resting rates after vagotomy to be from 42 to 96 beats per minute faster than after the previous removal of the accelerators. The wide differences in these figures is largely due to the differences in time of the observations after vagotomy. They all show the existence of a marked vagal tone. The figures all fall short of the rates observed when the vagal endings were blocked by atropine after removal of the accelerators, but this is to be expected since the latter observations were made immediately after the administration of the atropine while the automaticity of the heart was still at its maximum.

2. The reaction to muscular exercise. — Much to our surprise the dogs showed a marked acceleration on exercise after all the extrinsic cardiac nerves were cut. These accelerations varied somewhat in different animals, and differed greatly in the same animal on different days. The accelerations on the first day, a few hours after the vagotomy, were very high, but by the end of the second day the accelerations due to the same amount of exercise had become greatly reduced. Thus dog No. 4 increased his pulse rate 64 beats per minute on the day of vagotomy, but on the day following, the same amount of running gave an acceleration of only 18 beats. Similarly dog No. 6 accelerated 68 beats per minute at first and on the next day only 12 beats. The time of exercise was reduced from two minutes to thirty seconds in these experiments on account of the marked cyanosis and vomiting which were present immediately following vagotomy. It will be noted that the accelerations immediately following vagotomy were greater than those observed before any of the

nervous mechanisms were removed. Results similar to these were obtained on four of the six dogs. The data on two of the dogs were incomplete since our attention had not yet been called to this point.

The fact that the accelerations immediately following vagotomy were at times higher than in the intact animal suggested to us that possibly an entirely new factor had been introduced. It was observed that the dogs exercised on the same day that the vagotomy had been performed became extremely cyanotic, due to the slow respiratory rate and the almost entire inability of the respiratory organs to meet the demands of the moment. On the day following the operation, however, the respiratory exchange seemed to be sufficiently adequate to prevent any marked cyanosis during the same amount of exercise. Just how this improvement was brought about we are not entirely clear. In part it seemed to consist of a slight permanent increase in rate and the ability to accelerate a few respirations per minute during the exercise. Such an acceleration does not necessarily conflict with the conclusions of Scott,¹³ who showed that after vagotomy the rate of respiratory discharge could not be raised by increasing the carbon dioxide content of the blood. Psychic impulses or even temperature of the blood might have had an effect in our animals. Stewart and Pike¹¹ cite the case of a dog in which on emotional excitement the respiratory rate increased after vagotomy. Whatever the means of adaptation may have been in our animals the same amount of exercise on the second or third day following vagotomy gave very few of the distressing cyanotic symptoms observed during the same procedure shortly after the operation. Along with the disappearance of the cyanosis, retching and vomiting, the exercise acceleration showed its marked decrease.

It seemed, therefore, that the great acceleration occurring at first might be due to the asphyxia. That this was the case we proved on dog No. 6. On the day following vagotomy when the pulse rate could only be increased 12 beats by the same exercise that on the day before had given an increase of 48, the dog was asphyxiated for 30 seconds. This was done by wrapping a wet towel around his head. The struggling during this procedure was probably no more than equivalent to the exercise previously

given, but the pulse rose to 208 per minute, thus almost attaining the frequency observed when exercise was given immediately after vagotomy. Evidently the marked accelerations observed after vagotomy were in some way associated with asphyxia.

The recent work of Von Anrep,¹⁴ who showed that there is a secretion of the adrenals during asphyxia arising through stimulation of the centres of their secretory nerves, suggested a possible explanation of this asphyxial acceleration. The hypothesis could readily be put to a crucial test. When dog No. 6 was made to exercise for thirty seconds by struggling during asphyxia its heart accelerated 92 beats per minute. If ligation of the blood vessels to the adrenal glands should prevent this acceleration, the conclusion would be justified that the acceleration was due to a secretion of the adrenals. This experiment was therefore performed. The blood vessels were tied under ether anaesthesia. The animal was allowed to recover, and exercise during asphyxia was tried one and one-half hours after the operation, before the intervention of the marked asthenia which follows removal of the adrenals in dogs. The marked acceleration was now absent. Asphyxia and struggling for 90 seconds produced an acceleration of only eight beats per minute. This acceleration may be attributed to temperature and it shows how relatively small a role that factor plays. That this lack of acceleration was due to removal of the adrenals and not to depression following the operation, was shown by a similar experiment on a dog whose extrinsic cardiac nerves were intact. In this case although the resting pulse was 224 per minute and the dog had become very asthenic and would exercise but little, the heart still accelerated to 248 beats per minute.

The marked acceleration which was observed during exercise immediately after all the extrinsic cardiac nerves were cut was therefore due largely to a secretion of the adrenals. As shown by Eyster and Meek,¹⁵ the action of the adrenalin is independent of the integrity of the accelerator nerves. The acceleration found on the second and third day after the vagotomy, when the signs of asphyxia were reduced or absent, remains to be explained. The greatly reduced power to accelerate at this time indicates clearly the importance of the role which the inhibitory mechanism

had been playing. Gangliectomized dogs that accelerated on an average of 41 beats per minute after two minutes exercise were able after a subsequent vagotomy to accelerate only 16 beats per minute, provided there were no signs of asphyxia. The inhibitory mechanism was then responsible for the major part of the acceleration observed after extirpation of the accelerators.

To explain the limited acceleration possible after the signs of asphyxia had passed off, four possibilities suggest themselves, namely: changes in blood pressure, respiratory rate, temperature, or composition of the blood.

A review of the literature shows quite clearly that the blood pressure has no effect on the isolated mammalian heart, and that in those experiments which seem to show the contrary the temperature was not controlled. It was first shown by Martin¹⁶ that between the pressure limits of 30 and 150 millimetres of mercury the pulse rate is not in the least influenced, provided the composition and the temperature of the perfused blood were kept constant. The recent work of Knowlton and Starling¹⁷ confirms this result.

In a large percentage of animals whose hearts are normally slowed by tonic activity of the vagi, such as the dog, there is an acceleration of the pulse which occurs synchronously with inspiration. It would be expected, therefore, that when the respiratory rate increased an acceleration of the pulse rate would result. This could hardly explain the increase in our experiments, however, for the simple reason that the increase in respiratory rate after vagotomy was at most very little and in several cases showing the usual slight acceleration it did not occur at all.

However, to rule out completely any mechanical or nervous effects on pulse rate arising from vagal breathing simultaneous records of the respiration and heart beat were made by means of a pneumograph and the string galvanometer. The speed of the records was made such that measurements to .01 second were possible. No differences occurring synchronously with changes in respiratory phase could be discovered. A further investigation was then made of the lengths of the heart cycles when the respiration was increased in rate and depth. For this purpose 2.5 c.c. of M/50 NaCn. was injected in the ear vein of

the unanaesthetized animal. The amplitude of respiration was much increased and the rate rose from 5 to 12 per minute. In spite of these increases no effect was observed in any stage on the length of the cardiac cycle.

Of the two products of muscular activity which could produce changes in other parts of the body by altering the condition of the blood, heat and metabolic products, attention was paid only to the latter in the earlier work on exercise. Johansson⁷ attributed the comparatively small accelerations that he obtained when the hind limbs were tetanized by stimulation of the lumbar cord to fatigue products, but furnished no proof for this assumption. Hering,⁶ whose paper appeared shortly after that of Johansson, suggested that this might be the cause of the accelerations he obtained after the inhibitory and accelerator nerves to the heart were cut. The experiments of Johansson were confirmed by Athanasiu and Carvallo,² who, however, present no additional evidence that products of metabolism were the real cause. It has, however, been rather generally accepted that at least in prolonged exercise the effect of fatigue products directly on the heart is added to the acceleration which has already resulted through the nervous system.

Considerable doubt has been thrown on this view by recent work. Mansfield found that intravenous injection of the extract of fatigued muscle produced no more cardiac acceleration than a corresponding amount of the extract of normal muscle. We have already mentioned the work of Petersen and Gasser, who found that while substances are formed in the fatigued muscle which affect the size of the beat, these substances are without effect on the rate. We must, therefore, next consider the temperature change produced by exercise as a possible explanation of the acceleration in pulse rate occurring after all nervous connections are severed.

While it has been known since the experiments of Newell Martin that the rate of the isolated heart increases as the temperature rises and decreases as it falls, little attention has been paid to it in the problem of the acceleration during exercise. This is probably largely due to the fact that it has been found that the temperature curve does not closely parallel the curve of heart

rate. It is by the work of Mansfeld⁵ that interest has recently been revived in temperature changes. However, according to his view, the action of heat is not expressed merely in the increased chemical activity of the heart, but the change in temperature stimulates the endings of afferent vagal nerve fibres in the heart which produce a reflex stimulation of the accelerator centre. This conclusion is based on the fact that when the hind limbs of his animals were isolated from the central nervous system and tetanized, he obtained marked accelerations if the temperature of the animal was kept above 36 degrees. These did not occur when the reflex arc was cut.

Application of this theory to our observations shows how far it falls short of explaining the facts. In the first place the accelerations in our animals were as good after the removal of the stellate ganglia as before, which according to Mansfeld's theory, would be impossible since the efferent neurone of the arc he describes was interrupted. In the second place, the heart has considerable ability to accelerate still left after both the accelerator and inhibitory nerves are cut, which, if due to the rise of temperature, must be caused by a direct action.

The rise of temperature in our experiments observed after the two-minute period of exercise was in most cases .4° to .5° C. In the isolated heart Martin found that for temperatures between 37° C. and 40° C. a variation of one degree in the perfusion fluid changed the heart rate from 5 to 18 beats per minute. The figures published by Knowlton and Starling gave increases of 3 to 12 beats per minute for similar conditions. Increased temperature of the blood may be somewhat more effective in the intact animal than in case of the isolated heart. If a slight advantage of this kind is granted the accelerations we have obtained after removal of all nervous connections and after asphyxial effects have abated is quite sufficient to explain the residual acceleration, averaging 16 beats per minute, which we have observed.

III. EFFECTS OF EXERCISE AFTER CUTTING THE VAGI ALONE

An attempt was made to study in a positive way the part played by the accelerators in the early acceleration of exercise.

To do this dogs were vagotomized and a day later the adrenals were ligated. As was to be expected, exercise immediately after the vagotomy produced cyanosis and vomiting with a very rapid heart rate. In one case, dog No. 10, the pulse increased from a resting rate of 160 per minute after vagotomy to 224 on exercise. From our previous experience it seemed impossible to tell whether this increase was due to an asphyxial secretion of adrenalin or to a stimulation of the accelerator mechanism. This point we tried to settle by tying off the adrenals and again exercising.

Two hours after extirpation of the adrenals while the dog was in good condition, the same amount of exercise increased the pulse from a resting rate of 160 to 184. It was noted that the maximum increase occurred in the third and fourth quarter minutes after a 30-second period of exercise, which was of course typical of accelerator stimulation. The increased rate after removal of the adrenals was about one-half that observed in the normal animal. A second experiment verified the findings just mentioned, the acceleration after removal of the adrenals being, however, somewhat less. The loss of the inhibitory mechanism seems, therefore, to interfere more with exercise acceleration than does the loss of the accelerators. The definite acceleration after section of the vagi and extirpation of the adrenals shows, however, that although the accelerators may not play a leading part in the intact animal, yet it is possible through them to cause an increase in pulse rate.

IV. DISCUSSION

Our work has led us to believe that the heart as a result of exercise may under certain conditions be accelerated in at least four different ways; namely, by a decrease in vagal tone, by stimulation of the accelerators, by a secretion of adrenalin and by an increase in the temperature of the blood. Just what part does each of these factors play in the increased pulse rate following ordinary voluntary exercise? Before attempting to answer this question one should have clearly in mind that there are apparently two types of acceleration following exercise, one immediate and the other prolonged. Our experiments and our conclusions apply only to the immediate response of the heart.

The cause of the increased heart rates, which may persist for long periods after exercise has ceased, seems to us to be a separate and distinct problem.

The rapidity with which acceleration of the heart rate follows exercise as shown by Bowen, Buchanan and ourselves, the vagal character of the acceleration as pointed out by Hunt and Aulo, and the fact shown by our work that the reaction of the heart to exercise is impaired by removal of the inhibitory mechanism but practically unaffected by extirpation of the accelerators, all seem to give ample proof that the first acceleration during exercise in the normal animal is produced by inhibition of vagal tone. Our data give no evidence as to whether this inhibition is brought about by an irradiation of motor impulses in the medulla according to Johansson, or whether it is a reflex from peripheral muscular end organs according to Athanasiu and Carvallo. The marked acceleration found after extirpation of the stellate ganglia does, however, invalidate any explanation depending on the accelerators as part of the reflex arc.

Inhibition of the tone of the vagus is the most economical means by which acceleration of the heart can be brought about. On account of the great differences in rate demanded of the heart in different states of bodily activity, the potential automaticity of the heart is high but is held in check by the central nervous system through the vagal inhibitory mechanism. This potential automaticity, which may be defined as the maximal rate of impulse formation when the heart is free from all control, is more than sufficient to allow for the accelerations occurring during exercise. By releasing the check on this automaticity, the acceleration in rate demanded by increased activity can readily be produced. An analogy may be drawn with a battery circuit in which the amount of current is controlled by a resistance box. If an increased current is demanded which is still less than the battery is able to produce, the most logical procedure would be to remove some of the resistance rather than to add more batteries.

The accelerator mechanism might be regarded as a factor of safety superimposed on the vagus to meet the stress of extreme conditions. The fact that it can produce a certain increase in

heart rate after section of the vagi and ligation of the adrenals would be in accordance with such a view. It was brought out in Hunt's work that the accelerator mechanism is very resistant to pathological conditions such as low blood pressure, asphyxia, and drugs such as curare and the anaesthetics. The recent work of Kuntz¹⁸ on the development of the sympathetic nervous system in vertebrates is of interest in this connection. He found that the vagal sympathetic plexuses were the first to arise in the course of evolution and only as specialization advanced was any part in the nervous control of the internal functions shifted posteriorly. If this be true it follows that the accelerator mechanism is added to the phylogenetically older inhibitory mechanism.

The part played by temperature in the acceleration immediately following exercise must be small. For this factor to affect the heart a comparatively long latent period is necessary. When, however, the blood of the body finally reaches a higher temperature, it must have its effect on the heart rate. This influence may be important in prolonged exercise but ordinarily it is added to the vagal effect and thus obscured. Our experiments show that accelerations from this cause could not exceed about 16 beats per minute.

The amount of acceleration that is due to the secretion of adrenalin in the intact animal is probably negligible. As is well known, when the vagi are intact the injection of adrenalin is followed by a slowing of the heart due to action either directly or reflexly on the cardio-inhibitory centre. Exercise with dyspnoea would doubtless call forth a secretion of adrenalin in the normal animal, but so far as we know with the vagi intact this would not express itself in an increase of heart rate. It might, however, be useful and important in augmenting the strength of the beat. In this way the heart might be benefited by the secretion of adrenalin which Cannon and de la Paz¹⁹ have shown to occur at times of great emotion. That exercise as such has little effect on the adrenals has already been shown in our experiments. After the asphyxia succeeding vagotomy had somewhat abated, the same amount of exercise no longer greatly accelerated the heart.

SUMMARY

Acceleration of the heart at the beginning of voluntary exercise in the normal animal is chiefly due to the decrease in tone of the cardio-inhibitory centre. Our evidence for this conclusion is the following: (1) Electro-cardiograph records confirm the work of Bowen and Buchanan that acceleration takes place as early as the cardiac cycle following the initiation of the exercise. (2) Acceleration of the heart at the beginning of exercise persists after the removal of the accelerator mechanism. The actual increase in number of beats due to a given amount of exercise has been found to be practically the same in six dogs before and after removal of the stellate ganglia. One of these animals was observed for over four months. (3) Acceleration on exercise is reduced after section of the vagi provided that all asphyxial effects are excluded.

After the removal of the accelerators and subsequent section of the vagi marked acceleration of the heart may still be produced by a short period of exercise. This is associated with the cyanosis following vagotomy and on the second day when the animal is able to do the same work without such a marked cyanosis the increase following exercise is greatly reduced. It may be increased again by asphyxiating the dog for some 30 seconds. After tying off the adrenals neither asphyxia nor exercise gave a marked increase in heart rate. Exercise involving asphyxial conditions may then be accompanied by a secretion of the adrenals. In the normal animal with the vagi intact this secretion of adrenalin can hardly be supposed to affect the heart rate. It may, however, cause an increase in the amplitude and force of contraction.

In all six dogs the heart rate after removal of the accelerators was found to be remarkably constant, averaging about 72 beats per minute. The resting pulse rate of each animal is therefore believed to depend more on accelerator tone than on any other factor.

After removal of all nervous control and elimination of the adrenals exercise may still cause a small acceleration of the heart. This is attributed to the increased temperature of the blood.

Acceleration of the heart occurs on exercise after vagotomy

and extirpation of the adrenals. The amount though small is more than can be accounted for by increased temperature of the blood. Acceleration may therefore be brought about through the accelerators if necessary. Our work leads us to believe that the accelerators are a factor of safety and that in exercise their action is superimposed on that of the vagi only in times of great need. Aside from this their chief function is maintaining the level of the resting pulse.

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THE NERVE CONTROL OF THE THYROID GLAND¹

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TWO mechanisms are established within the animal body by means of which the functions of its different parts are co-ordinated. One of these acts through the medium of the nervous system, while the other is chemical in nature. The two are, however, interdependent to some degree. The activities of the nervous system in this respect have long been a subject for accurate investigation, but the work of recent years has served to emphasize the importance of the hormones, the chemical messengers by means of which widely separated structures are brought into a harmony of action. At some link in the chain it will be found, however, that the determining influence of the nervous system is predominant.

The thyroid gland is a favorite example of the glands which produce internal secretions. Its functions and pathological conditions are perhaps better known than any others in its class. Variations in its functions are correlated with fairly well-defined clinical conditions. A large number of studies have been made upon the chemical nature of its active substance, and many attempts have been made to show how its activity is regulated, at least in part, by the secretions of other ductless glands.

It seems very probable that the active substance in the thyroid gland contains iodine in combination with protein, and that the physiological activity is in proportion to the quantity of iodine in the combination. We believe that the function of this substance is not performed within the gland itself. The colloid of the gland may be looked upon as reserve material ready for dis-

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charge into the blood or lymph, through which medium the general tissues of the body are supplied. Some attempts have been made to demonstrate the presence of this active substance in the blood by means of a biological reaction, but none of them have thus far been successful. If one considers how very vascular the gland is, and how small a quantity of the active substance is distributed through the blood leaving the gland in twenty-four hours, it is not surprising that none of these methods have satisfactorily demonstrated the presence of the iodized protein in the circulation.

Recently Asher and Flack¹ have attempted to demonstrate the nerve control of the thyroid. Their experiments are indirect and are so complicated as to leave the matter in great doubt. Their experiments were made upon rabbits, cats and dogs, with a view to determine whether any phenomena could be observed after stimulation of the thyroid nerves which would lead to the conclusion that stimulation had caused an increase in thyroid secretion in the blood. As a means to this end they compared the excitability of the depressor nerve before and after stimulation of the thyroid nerves, and also the effect of a small intravenous injection of adrenalin before and after such stimulation. They conclude that under otherwise exactly similar experimental conditions, a stimulation of the depressor nerve or an intravenous injection of adrenalin was more effectual during a stimulation of the thyroid nerves than shortly before without it. That both these symptoms, viz., increased depressor excitability and more effective action of adrenalin, actually depend upon an inner secretion of the thyroid and not upon any accompanying circumstance of nerve stimulation is proven by the fact that on extirpation of the thyroid the symptoms no longer appeared, and on the other hand intravenous injections of thyroid extracts acted exactly like stimulation of the thyroid nerves. Their experiments are complicated and while suggestive they do not satisfy.

The purpose of the experiments reported in this communication is to give evidence of a different character that the thyroid gland is, at least in part, under nerve control. Briefly, the plan of the experiments was to determine, first, whether the iodine content of the two lobes of the normal thyroid gland from the

same animal is identical; and second, whether stimulation of the nerves leading to one lobe causes a loss in its iodine content. If the two lobes of the normal thyroid are identical in iodine content they may serve as controls of one another. Granting such to be the case it was our hypothesis that stimulation of the nerves to one lobe might cause a change in the iodine content because of the resulting discharge of iodized proteid from the gland.

The method followed in determining the iodine in all the analyses herein reported was the modification of the Baumann process devised in this laboratory by Riggs.² Some very slight changes in the technique were made which experience has shown to be valuable in rendering the fusion easier and in lessening the tendency to form iodates to such a degree that many of the fusions were wholly free from such compounds. The procedure in detail was as follows: the fresh glands were carefully trimmed from any adhering tissues and accurately weighed; they were then placed in a nickel crucible and covered with 10 to 15 c.c. of a 50 per cent solution of sodium hydroxide. Heat was carefully applied and the glands disintegrated and finally fused. Such a technique is preferable to the use of the solid hydroxide in that it gives a gradual disintegration of the gland and allows carbonization to take place at a lower temperature. At no time was more than a dull red heat applied and often not that. When the mass had been thoroughly fused, only as much sodium nitrate was slowly added as was necessary to oxydize any small particles of carbonaceous material remaining. After cooling, the fused mass was dissolved with hot water, quantitatively filtered, made up to exactly 100 c.c. and thoroughly mixed. From this point the method of Riggs was followed exactly.

In this laboratory we have found that in determining such small amounts of iodine as is found in dogs' thyroids the method is preferable to that of Hunter,³ in that the fusion is more easily carried out, and it requires the use of fewer standardized reagents. In Kendall's⁴ method the fusion is quite similar except that he uses larger amounts of sodium hydroxide and potassium nitrate, and reduces excess by the use of gallic acid which in itself causes trouble if too much is added. His method for titration after fusion is more complicated than Riggs' colorimetric method and,

in this laboratory, has not been found more accurate when using minute quantities of iodine.

For the purpose of determining whether the iodine content of the two lobes of the thyroid is the same per gram of fresh gland several animals were killed and the glands immediately dissected out and subjected to the method outlined above. No particular selection was followed with reference to the animals, and in no case was there found any gross pathological condition of the gland. They were the usual animals kept in stock and had been fed the same diet which we have used for a number of years, viz. boiled beef hearts and bread.

Table I shows the results of these analyses:

TABLE I
SHOWING IODINE CONTENT OF THE TWO SEPARATE
THYROID LOBES FROM THE SAME ANIMAL

| Lobe | Weight of lobe | Milligrams Iodine found | Milligrams Iodine per gram of gland |
|------|----------------|----------------------------|---|
| R | 0.763 | 0.300 | 0.393 |
| L | 0.886 | 0.350 | 0.395 |
| R | 0.7048 | 0.475 | 0.674 |
| L | 0.6600 | 0.450 | 0.681 |
| R | 0.7174 | 0.700 | 0.975 |
| L | 0.7620 | 0.750 | 0.984 |
| R | 1.2786 | 0.900 | 0.7038 |
| L | 1.1400 | 0.800 | 0.7011 |
| R | 1.0956 | 1.100 | 1.004 |
| L | 0.9872 | 1.000 | 1.012 |
| R | 0.9810 | 1.440 | 1.468 |
| L | 0.8154 | 1.200 | 1.472 |
| R | 0.3602 | 0.132 | 0.3664 |
| L | 0.4020 | 0.145 | 0.3607 |

From the table given it is evident that the iodine content varies widely in the different animals, but the two lobes are wonderfully constant, the difference shown falling within the limit of error of the analytical method. The largest difference

noted is found in the third pair of glands, in which there is a difference of only .009 mgms. per gram of fresh gland.

The figures are based upon the weight of the fresh gland rather than of the dried substance, because most analyses of the iodine content of these glands recorded in the literature are so expressed, and furthermore because it is probably more accurate. It is not a simple matter to dry the glands to constant weight and transfer the dried powder without loss to a fusion crucible, and the fusion of the moist gland in the manner described above is much simpler.

It seems evident from the analysis quoted that one lobe of the thyroid may serve as control of the other provided both lobes are normal.

The method of conducting the stimulation experiments was as follows: The stimulation in each instance was electrical and was obtained by connecting three dry cells in series for the primary current. This current was connected with the ratchet wheel of a clock in such a manner as to permit a momentary stimulus every ten seconds. The current from the secondary coil was so regulated that only a faint stimulus was given to the moist tongue of the operator.

The nerve supply to the thyroid probably has its origin in filaments from the sympathetic. In man a nerve filament can be demonstrated to arise from the superior cervical ganglion of the sympathetic, and to follow more or less closely the course of the superior thyroid artery, and to terminate in the upper anterior portion of the superior pole of the thyroid. In addition there are microscopic filaments from the sympathetic which can be demonstrated to enter the gland in the walls of both the superior and inferior thyroid arteries and sympathetic filaments are apparent around each of the thyroid vesicles.⁵

In the dog the same nerve filament exists entering each of the separate thyroid lobes near the outer superior pole, but the cervical sympathetic and the pneumogastric nerves form one strand and the apparent nerve supply of the gland cannot be proved by dissection, as in man and the cat, to arise only from the sympathetic. Nevertheless it is possible that the dog's anatomy is not different from that of the cat and man in this respect.

In these experiments ether anaesthesia was used in each case and was administered through a bottle with a cannula in the trachea. The method of arranging the stimulation was varied in the different experiments.

STIMULATION EXPERIMENTS — SERIES I.

In these experiments one lobe of the gland was removed immediately before the stimulation was begun. This lobe served as a control. The vessels of the upper pole of the remaining lobe were carefully separated from the connective tissues and the electrodes were then carefully brought into contact with the vessels and the accompanying nerve filaments. Careful approximation of the electrodes was carried out so that the blood supply and return would not be impaired.

(In the fifth experiment in this series both lobes were left in until the end of the period of stimulation.)

TABLE II

SHOWING IODINE PER GRAM OF CONTROL AND STIMULATED GLAND. SERIES I.

| Gland | Wt. of gland grams | Iodine in mgms. per gram | Length of stim. |
|---------|-----------------------|-----------------------------|--------------------|
| Control | .485 | .2051 | 2 hrs., 30 m. |
| Stim. | .417 | .1923 | |
| Control | .4062 | 1.1078 | 3 hrs. |
| Stim. | .3717 | 1.0088 | |
| Control | 1.0680 | .8895 | 3 hrs. |
| Stim. | 1.1234 | .7566 | |
| Control | 1.2280 | 1.3029 | 3 hrs. |
| Stim. | 1.2000 | 1.0417 | |
| Control | .6564 | .9012 | 2 hrs., 30 m. |
| Stim. | .5770 | .7312 | |

The average loss in iodine was .1351 mgms. per gram of gland, but in that case No. 4, in which the iodine content of the control gland was highest, the loss on stimulation was .2612 mgm. iodine per gram of gland, a loss of approximately 20 per cent. In every

stimulated gland there has been a loss so great as to be beyond the possibility of error in the determination.

STIMULATION EXPERIMENTS — SERIES II

In these experiments both lobes remained intact throughout the experiment. After the period of stimulation they were both removed and prepared for analysis. The point of stimulation was on the combined vagus and sympathetic. The vagus on the side stimulated was ligated low down on the neck, a careful dissection was made, the superior ganglion exposed, and the nerve cut central to the ganglion. The electrodes were applied to the nerve peripherally to the ganglion. The exposed tissues were covered with cotton moistened with Locke's solution.

TABLE III
SHOWING IODINE IN MILLIGRAMS PER GRAM OF GLAND AFTER STIMULATION
THROUGH NERVE

| Gland | Wt. of lobe in grams | Iodine in mgms. per gram of gland | Time of Stim. |
|---------|-------------------------|--------------------------------------|---------------|
| Control | 2.7573 | .1813 | 2 hrs., 30 m. |
| Stim. | 2.5273 | .1582 | |
| Control | .6174 | .3239 | 3 hrs. |
| Stim. | .8126 | .1723 | |
| Control | 1.0646 | 1.3620 | 2 hrs., 15 m. |
| Stim. | 1.2070 | 1.0270 | |

The analytical results in this series show a larger percentage loss of iodine than in those quoted in the previous experiment. In the second animal nearly 50 per cent of the iodine in the stimulated lobe was discharged into the blood or lymph during the period of stimulation.

STIMULATION EXPERIMENTS — SERIES III

In this series the thyroids were both left intact until the termination of the experiment. The combined vagus and sympathetic were isolated about one inch below the thyroid cartilage

and the stimulation which was identical with that used in the previous experiments was applied at this point. The nerve was not cut or ligated in any manner. The circulation through the gland was not impaired or disturbed by the operative procedure.

TABLE IV

SHOWING LOSS OF IODINE IN GLANDS STIMULATED THROUGH THE INTACT NERVE

| Lobe of gland | Weight in grains | Iodine in mgms. per gram | Loss | Time |
|---------------|------------------|--------------------------|------|---------|
| Control | .9469 | .581 | | 45 min. |
| Stim. | .8048 | .559 | .022 | |
| Control | 2.8732 | 2.866 | | 3 hrs. |
| Stim. | 3.1000 | 1.967 | .899 | |
| Control | .5228 | 2.486 | | 3 hrs. |
| Stim. | .5008 | 2.196 | .290 | |
| Control | .7450 | 2.013 | | 3 hrs. |
| Stim. | .5425 | 1.843 | .170 | |
| Control | .4450 | .272 | | 30 min. |
| Stim. | .6660 | .241 | .031 | |
| Control | .4738 | 2.216 | | 3 hrs. |
| Stim. | .6647 | 2.031 | .185 | |
| Control | .7830 | 1.277 | | 3¼ hrs. |
| Stim. | .8730 | 1.027 | .250 | |

SUMMARY

The experimental results may be summarized in the following way:

1. The average difference of iodine, expressed in mgms. per gram of fresh gland, between the two thyroid lobes of seven normal dogs was .0055 mgms.
2. The average difference found when the superior vessels, with accompanying nerve fibres, of one lobe were stimulated was .1351 mgms.
3. The average difference found when the stimulus was applied to the vagus peripherally to the superior ganglion, the nerve being cut central to the ganglion and ligated peripherally to the stimulus, was .1699 mgms.

4. The average difference found when stimulus was applied to the intact vagus was .2640 mgms. In series III two glands were stimulated 45 minutes and 30 minutes respectively. If the loss in the remaining five glands which were stimulated three hours is averaged it will be found that a loss of .3588 milligrams per gram of gland occurred.

In no case did we fail to get a loss after stimulation. There seems to be no reasonable doubt from these results that the thyroid is at least in part under nerve control, and that its physiologically active substance is discharged into the circulation in response to a nerve stimulus.

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² RIGGS: *Journal of the American Chemical Society*, 1910, xxxii, p. 692.

³ HUNTER: *Journal of Biological Chemistry*, 1910, vii, p. 321.

⁴ KENDALL: *Journal of the American Chemical Society*, 1912, xxxiv, p. 894.

⁵ RHINEHART: *American Journal of Anatomy*, 1912, xiii, p. 91.

THE VARIABILITY OF BLOOD PRESSURE AND OF VASOMOTOR IRRITABILITY IN THE ANAESTHETIZED DOG

BY R. G. HOSKINS AND HOMER WHEELON

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IN connection with other researches we have found it necessary to determine somewhat definitely the extent of variation of blood pressure and of vasomotor irritability at different times in the individual anaesthetized dog, under ordinary laboratory conditions. The matter seems to have received little exact investigation. Pawlow,¹ however, has reported an instance of a dog in which an arterial cannula was left for a number of days. He made several blood pressure determinations, but without anaesthesia. The pressure at different times proved remarkably constant. A series of readings during twenty-one days showed pressures of 128, 131, 128, 129, 131 millimetres of mercury. As regards changes of vasomotor irritability some data have been secured in the use of the blood-pressure method of assaying epinephrin. Under the conditions of any given experiment there is a considerable degree of constancy in the reactions to this drug. The literature on the subject has been reviewed by Schultz.² We are not aware, however, of any previous determinations in the same animal at different times.

Our experiments were made upon medium sized dogs, about 10 kilos in weight, with the exception of one which weighed 17 kilos. Males or females were taken at random. Two or three blood-pressure determinations were made on each animal. An interval of five to ten days between successive determinations

¹ PAWLOW: Archiv für die gesammte Physiologie, 1879, xx, p. 216.

² SCHULTZ: Bulletin No. 61 Hygienic laboratory, public health and marine hospital service of the United States, 1910.

permitted recovery from the preceding operation. As Poiseuille¹ showed nearly a century ago there is little difference in mean pressures in the larger arteries, consequently any of these could have been used. Owing to their accessibility, however, we used the right and left femorals and a carotid. Blood pressure was recorded by means of an ordinary mercury manometer and float.

Ether administered by the open cone method was used throughout the series. It is of course possible by varying the depth of anaesthesia to produce marked differences in arterial pressure. On the other hand, if the anaesthetic is carefully administered in amount just sufficient to keep the corneal reflex in abeyance, a long-continued record can be secured in which the pressure is practically constant. It was at this depth of anaesthesia we aimed to work. In the earlier experiments each dog was given an injection of morphine, 0.1 to 0.2 grain, the amount being constant for any given animal. It was found, however, that this procedure added little to the smoothness of the anaesthesia and it was discontinued.

To permit a series of observations in the same animal aseptic precautions were observed in making the determinations. In securing an aseptic technique the use of a Hall reservoir cannula proved fortunate. This cannula was devised by Dr. W. S. Hall to obviate the necessity of a pressure flushing system. It consists of an ordinary glass arterial cannula in which is blown a bulb of about 20 cc. capacity. This is filled with anti-coagulating solution and connected directly with the manometer. To prevent too rapid diffusion into the artery but at the same time keep the fluid supplied to the blood in sufficient amount, the part of the cannula below the bulb should be conical in shape and the lumen of the apex comparatively small. With reasonable expedition in carrying out the experiments little trouble with clotting is experienced. In the earlier observations half-saturated solution of sodium carbonate was used as anti-coagulant. A single charging with this prevented coagulation for an hour or longer. Direct experiments showed that no immediate deleterious results followed; the post-operative mortality rate, however, was high. Substitutions

¹ POISEUILLE: Thèse de Paris, 1828. Cit. by Tigerstedt, *Physiologie des Kreislaufes*, Leipzig, 1893, p. 351.

of 5 per cent solution of sodium citrate greatly lowered this rate without seriously impairing the efficiency of the method. Occasionally, however, a cannula had to be removed and recharged.

All necessary fluids and appliances having been sterilized, the dog was prepared for an aseptic incision; the hair was removed with saturated solution of sodium sulphide. The skin was then washed with soap and water, rinsed with alcohol, dried and swabbed with tincture of iodine. An artery and a vein were laid bare and cannulas inserted into each. To prevent necrosis and subsequent sloughing it is desirable to protect the exposed tissues from contact with the anti-coagulant solution.

When working with femoral vessels it is desirable to insert the cannulas about 10 cm. distal to the inguinal ligament. In two instances in which the incision and subsequent ligation were made close to the body gangrene followed. When the incision was made in the neck no untoward results followed ligation of one carotid artery and external jugular vein.

To test the vasomotor irritability intravenous injections of standard doses of "adrenalin" and of nicotine were made. To secure uniform freshness and sterility of the adrenalin it was bought in 1 c.c. ampoules. There was, therefore, little or no variability of the standard due to deterioration in an open bottle. Further to prevent decomposition of the adrenalin, distilled water was used as a diluent. After experimenting with various dilutions and dosages we finally selected as standard 0.66 c.c. and 1.33 c.c. (10 and 20 minims) of 1:100000 solution. It was found that doses below 10 minims gave notably less constant results than those of this size. On the other hand if the vagi are intact quantities larger than 20 to 30 minims are not advisable. With larger doses a reflex inhibition of the heart occurs so that the quantitative relationship between the dosage and its pressor effect is less direct.

The reaction to adrenalin varies greatly according to the speed with which it is injected. To secure uniformity in this respect the following technique was employed: To the venous cannula was connected a reservoir of normal saline solution by means of a rubber tube which was closed by a clip just above the cannula. By means of a hypodermic syringe the epinephrin was quickly

TABLE I

Showing Mean Blood Pressure, Maximum Percentage of Deviation from Average Mean and Maximum Percentage of Deviation from Average in Each Instance. Based upon 46

| Dog No. | 3 | 4 | 7 | 9 | 10 | 11 | 14 | 15 | 16 | | |
|---------------------|---------------------|---------|-------|-------|------|-------|------|------|------|-------|----|
| Weight in kilos | 9.5 | 7.9 | ? | 9.3 | 13.5 | 9.4 | | 12.2 | 10.3 | | |
| Sex | M | M | F | M | M | M | M | F | F | | |
| Blood pressure | R. Femoral | 148 | 120 | 136 | 136 | 108 | 112 | 110 | 120 | 90 | |
| | L. Femoral | 150 | 120 | 142 | 132 | 100 | 112 | 118 | 126 | 114 | |
| | Carotid | | 122 | 153 | | 128 | | | | | |
| | Average | 149 | 120.6 | 143.6 | 134 | 112 | 112 | 114 | 123 | 102 | |
| Maximum deviation | | 0.7% | 1.2% | 6.6% | 1.5% | 14.3% | 0% | 3.5% | 2.4% | 11.8% | |
| Adrenalin injection | Dosage ¹ | 1.33 | 1.33 | 2.66 | .53 | .53 | 1.33 | .53 | .80 | .80 | |
| | Pressor Effect | R. Fem. | 8 | 11 | 13 | 18 | 20 | 20 | 32 | 26 | 40 |
| | | L. Fem. | 10 | 8 | 10 | 28 | 15 | 24 | 30 | 32 | 40 |
| | | Carotid | | 20 | 14 | | 16 | | | | |
| | Average | 9 | 13 | 12.3 | 23 | 17 | 22 | 31 | 29 | 40 | |
| | Maximum deviation | 11% | 54% | 19% | 22% | 18% | 9% | 3% | 10% | 0% | |
| Nicotine injection | Dosage ² | .30 | .66 | 1.33 | .66 | .66 | 1.33 | .66 | | .66 | |
| | Pressor Effect | R. Fem. | 5 | 18 | 18 | 15 | 8 | 14 | 8 | | 19 |
| | | L. Fem. | 6 | | 18 | 14 | 8 | 24 | 14 | | 9 |
| | | Carotid | | 10 | | | 8 | | | | |
| | Average | 5.5 | 14 | 18 | 14.5 | 8 | 19 | 11 | | 14 | |
| | Maximum deviation | 18% | 29% | 0% | 3% | 0% | 26% | 27% | | 36% | |

¹ Expressed as c.c. of 1-100,000 solution.

² Expressed as c.c. of 1-5,000 solution.

injected into the tube just above the clip. At once this was released and the drug flushed into the vein as rapidly as it could pass through a large-bore cannula under a pressure of two feet of water.

Similarly injections of nicotine were made. The dilution was 1:5000 and the dosage 0.67 c.c. and 1.33 c.c. (10 and 20 minims). After a considerable number of records had been secured these were measured at random and the data pertaining to each animal segregated later. A wire was stretched the length of the record and by inspection the average mean pressure line throughout the experiment determined. The height of this line was then measured. The pressor effect of each drug injection was measured from the highest systolic point at the moment of injection to the

TABLE I

Pressure, Pressor Effect of Constant Doses of "Adrenalin" and Nicotine, Averages of Effects Determinations in 21 Anaesthetized Dogs. All Pressures expressed in Millimetres of Mercury.

| 22 | 23 | 26 | 27 | 28 | 29 | 31 | 32 | 33 | 34 | 35 | 36 | Average Deviation |
|------|-------|------|-------|------|------|------|------|------|------|------|------|-------------------|
| 3.8 | 10 | 7.8 | 10.1 | 9.5 | 13.6 | 9.5 | 7.7 | 8.2 | 11.6 | 11.8 | 17 | |
| F | M | F | M | M | F | M | M | F | M | M | F | |
| 10 | 113 | 100 | 108 | 102 | 136 | 98 | 112 | 126 | 86 | 136 | 128 | |
| 108 | | | 76 | 86 | | | 110 | | 94 | 158 | | |
| 116 | 114 | 85 | | | 150 | 98 | | 120 | | | 130 | |
| 112 | 113.5 | 92.5 | 92 | 94 | 143 | 98 | 111 | 123 | 90 | 147 | 129 | |
| 3.6% | 0.4% | 8.1% | 17.4% | 8.5% | 4.9% | 0% | 0.9% | 2.4% | 4.4% | 7.5% | 0.8% | 4.8% |
| 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | |
| 28 | 30 | 49 | 23 | 30 | 22 | 38 | 46 | 29 | 24 | 14 | 5 | |
| | | | 24 | 26 | | | 23 | | 26 | 18 | | |
| 26 | 26 | 42 | | | 12 | 33 | | 40 | | | 8 | |
| 27 | 28 | 45.5 | 23.5 | 28 | 17 | 35.5 | 34.5 | 34.5 | 25 | 16 | 6.5 | |
| 4% | 7% | 8% | 4% | 7% | 29% | 7% | 33% | 16% | 4% | 12% | 23% | 14% |
| 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | 1.33 | |
| 9 | 12 | 21 | 30 | 27 | 30 | 26 | 25 | | 15 | 14 | 10 | |
| | | | 26 | 27 | | | 23 | | 17 | 16 | | |
| 24 | 18 | 35 | | | 28 | 21 | | 32 | | | 9 | |
| 16.5 | 15 | 28 | 28 | 27 | 29 | 23.5 | 24 | | 16 | 15 | 9.5 | |
| 45% | 20% | 25% | 7.1% | 0% | 3% | 11% | 4% | | 7% | 7% | 11% | 15% |

highest point attained after it. Following dosages of adrenalin and nicotine of the size employed there results a secondary wave of subnormal pressure. It was thought that these depression waves might have some value as indices of the effects of the injections. The depressor effects, however, were found so variable for given dosages as to be useless as criteria.

A priori one would expect that blood pressure, a product of many variables, would show under the conditions of our experiments a wide variability. The actual determinations show, however, as biologic data go, a very fair degree of constancy. On account of the variability of dosages, weights, and breeds of dogs employed the results in different cases are not comparable with each other. The data are therefore not well adapted to mathe-

matical treatment. The essential point to the experiments, however, is the degree of variability from the average pressure in each case. In Table I is given the two or three pressures noted in each animal, the average pressure and the percentage of the maximum deviation from this average pressure in each dog. The average maximum deviation for the whole series can thereby readily be calculated.

The greatest variability was noted in case of dog 27, in which the higher and lower pressures were 108 mm. and 76 mm. respectively, giving a deviation of 17 per cent from their average value. In half the cases the deviation from the average was within $2\frac{1}{2}$ per cent of that average. The average deviation in the 21 cases was approximately 4.8 per cent from the average pressures.

The reaction to 20 minims of 1-100,000 adrenalin was more nearly constant than to the smaller doses employed. This quantity was finally selected, therefore, as giving the best index of vasomotor irritability. In a few of the earlier determinations, however, only smaller quantities were used. The data were tabulated just as were those previously considered: the pressor effect of each dose, the average in case of each animal, and the maximum percentile deviation from this average are given. Owing to the smaller numerical values the percentile deviations are notably higher than in the preceding series of data. The greatest variation from the average reaction was 54 per cent, in case of dog 4. The average maximum variation of the 21 cases was 14 per cent.

A priori one would expect a relationship between the existing blood pressure and the reaction to the standard dose of adrenalin. Such, however, does not appear in our determinations. Sometimes the reaction was greater with the higher initial pressure and sometimes smaller. In case of dog 27, with initial pressure of 108 mm., the reaction was 23 mm.; but with an initial pressure of 76 mm. the reaction was 24 mm., essentially the same as before.

The effects of the nicotine injections were tabulated just as in the preceding case. The reactions showed a similar degree of constancy. The greatest variability, — 45 per cent from the average, was noted in dog 27. The average maximum deviation of the series, 19 cases, was 15 per cent.

In many of the experiments an unexpected sort of constancy

was observed in the reactions to adrenalin and to a less extent in the reactions to nicotine. Following the injections there occurred a series of variable events giving for each animal what might be called a "reaction picture." These "pictures" consisted of various combinations of elevation succeeded by subnormal waves of pressure, of quickened or slowed heart beat, of augmented or depressed pulse pressure and of secondary tension waves. That such a concatenation of features would persist throughout a given series of injections is remarkable. Not only was this true, however, but the same reaction picture was often observed in a succeeding experiment several days later.

A practical difficulty in such experiments is to secure a uniform dosage of the drugs employed. Epinephrin is particularly susceptible to deterioration and the use of the same lot throughout a series of experiments is scarcely feasible. Moreover, the diluted solutions must be made up fresh for each experiment. Considering the high potency of the drug a certain degree of variability of strength of the final dilution is inevitable, even though the laborious plan were followed of starting each time with the dry crystals. Probably no greater error is introduced by using, as we did, a reliable commercial preparation and depending upon the manufacturers' standardization. The results obtained indicate, however, that this source of error is not of major importance.

The experiments as a whole show a fairly satisfactory degree of constancy and indicate that the method used is capable of giving a usable index of vasomotor activity and irritability and a corresponding criterion of the functional condition of the sympathetic nervous system.

SUMMARY AND CONCLUSION

1. Mean arterial blood pressure in the individual anaesthetized dog under laboratory conditions at different times is fairly constant. Forty-six determinations in 21 dogs at intervals of 5 to 10 days showed an average maximum deviation of 4.8 per cent. The greatest individual deviation from the average was 17 per cent.

2. The pressor effect of standard doses of epinephrin injected at different times is proportionately somewhat less constant. The

average maximum deviation from the average was 14 per cent in 21 animals. The greatest individual deviation was 54 per cent.

3. Similar results were secured with nicotine. The average maximum deviation was 15 per cent in 19 animals. The greatest individual deviation was 45 per cent.

4. The reaction consisted of a concatenation of features often giving "reaction pictures" characteristic for each animal.

5. The constancy of blood pressure and of the reactions to epinephrin and nicotine is of a degree to permit their use as criteria of activity and irritability of the sympathetic nervous system.

STUDIES IN FATIGUE

IV. THE RELATION OF ADRENALIN TO CURARE AND FATIGUE IN NORMAL AND DENERVATED MUSCLES

BY CHARLES M. GRUBER

[From the Laboratory of Physiology in the Harvard Medical School]

THAT certain drugs, i.e., atropine and pilocarpine or muscarine, curare and nicotine, curare and salicylate of physostigmin are mutually antagonistic has been shown by different experimenters.

In 1903 Brodie and Dixon,¹ in determining the point of action of adrenalin, used curare for paralyzing the nerve endings in smooth muscle. Very variable results were obtained by its use and they concluded that there was, therefore, a direct antagonistic action between curare and adrenalin, although only to a partial degree. Four years later Panella² observed that if curare was injected, either mixed with a small amount of adrenalin or followed by an injection of adrenalin, total paralysis did not result as it did when curare alone was injected.

In this paper I hope to show further that there is this antagonistic action and also that fatigue affects the threshold of a curarized muscle.

THE METHOD

In some cases the animals (cats) were decerebrated, in others they were anaesthetized with urethane (2 gm. per kilo body weight by stomach). In all instances they were tracheotomized. Usually the right tibialis anticus muscle, but in a few cases the left, was used for study.

¹ BRODIE and DIXON: *Journal of physiology*, 1903-04, xxx, p. 497.

² PANELLA: *Archives italiennes de biologie*, 1907, xlvii, p. 30.

Threshold stimuli were calculated in β units according to the Martin¹ method. The apparatus for this determination was connected to platinum needle electrodes thrust into the muscle. The strength of the primary current for determining the threshold of the normal muscle was .05 ampere and for the curarized and denervated muscle 1.0 ampere.

In every case the arterial pressure was recorded by a mercury manometer connected with the right carotid artery. After adrenalin was injected the blood pressure returned to normal, and after curare was injected the record became horizontal before the threshold was determined.

Through a cannula placed in the left external jugular vein the adrenalin was injected slowly in doses of 0.3 to 2 c.c. of a 1:100,000 solution. Through another cannula, placed in the right external jugular vein, the curare, in a 3 per cent solution, was injected slowly. As soon as natural respiration ceased, artificial respiration was begun and maintained throughout the experiment. For testing the effect of curare the radial nerve or the peroneus communis nerve was stimulated with a strong faradic stimulus.

Experiments were also performed on animals in which a section (2 cm. long) of the left peroneus communis nerve was removed aseptically 7 to 16 days before the experiment.

In experiments in which the muscle was fatigued the stimulating current was a maximal break induction shock obtained from a vulcanite disc interrupter, the rate of stimulation being 120 or 240 times per minute. This rate was kept uniform throughout each experiment. The animals for these experiments were always decerebrated and then fatigued from 10 minutes to one hour.

¹ MARTIN: Measurement of Induction Shocks, New York, 1912, pp. 71-93. For detailed description of the method employed in this work, see Gruber, this journal, 1913, xxxii, p. 438.

THE NORMAL THRESHOLD STIMULUS OF MUSCLE AS AFFECTED BY
CURARE, AND THE ACTION OF ADRENALIN OR FATIGUE
UPON THE CURARE THRESHOLD

Eight experiments were performed in which the average normal threshold for the tibialis anticus muscle varied from 12 to 26 β units or an average of 21 β units. This average is the same as that cited in earlier papers of this series.¹ After intervals varying from 15 minutes to one hour after an intravenous injection of curare, the animals completely immobilized, the threshold stimulus of the eight experiments increased from an average β of 21 to 65.7, an increase of 213 per cent. See Table I.

In the eight experiments performed adrenalin, *in 5 minutes or less*, decreased the average curare threshold of 65.7 β units to 38.9, a recovery of 60 per cent.

Figs. 1 and 2 are curves illustrating the effect of curare and adrenalin. These were plotted from the data of two of the experiments and show the relative heights of the threshold before and after an injection of curare and after an injection of adrenalin. In Fig. 1, points 1 and 2 represent the normal threshold stimuli. After the threshold at 2 was determined 2.5 c.c. of curare was injected intravenously, and 15 minutes later, with the animal immobile, the threshold was again determined (at 3). The injection of curare had increased it from 22.8 β units to 64.9, or 184 per cent. Five minutes after an injection of 2 c.c. of adrenalin (1:100,000) the threshold was decreased (i.e. at 4) from 64.9 to 42.5, a recovery of 53 per cent.

Fig. 2 also shows the relative heights of the threshold before and after an injection of curare and after an injection of adrenalin. In this figure the continuous line is the curve of the normal right tibialis anticus and the broken line that of the denervated left tibialis anticus of the same cat. The peroneus communis nerve was cut seven days previous to the experiment. In Fig. 2 (i.e. at 1 of the continuous line) the normal threshold was 24.3 β units. Eighteen minutes after injecting 3 c.c. of curare, when the animal was paralyzed this threshold was in-

¹ GRUBER: this journal, 1913, xxxii, p. 443; *Ibid.*, 1914, p. 335.

TABLE I
THE NORMAL THRESHOLD STIMULUS AS AFFECTED BY CURARE AND THE EFFECT OF ADRENALIN UPON THE CURARE THRESHOLD IN DECEREBRATE CATS. MEASUREMENTS TAKEN BY THE MARTIN METHOD. (I) NORMAL MUSCLE. (II) DENERVATED MUSCLE.

| I | | | | | | II | | | | |
|---|--------------------------------------|----------------|----------------|--------------------------------|----------------------|--|-----------------------------|----------------|----------------|--------------------------------|
| Number of c.c. of curare injected 3 per cent | Number of c.c. of adrenalin injected | Normal β | Curare β | Curare β after adrenalin | Increase in per cent | Recovery in per cent | Number of days degeneration | Normal β | Curare β | Curare β after adrenalin |
| 4.5 | 0.3 | 25 | 70 | 14.1 | 180 | 124 | 7 | 52.2 | 50.4 | |
| 4 | 0.4 | 26.4 | 72 | 35.6 | 173 | 80 | 8 | 93.2 | 53.8 | 70.5 |
| 3 | 0.5 | 24.3 | 77.6 | 43.2 | 219 | 64 | 7 | 50.0 | 50.8 | 50.8 |
| 3 | 1 | 12 | 41.2 | 30.7 | 243 | 36 | 8 | 59.6 | 53.6 | 45.8 |
| 2.5 | 2 | 14.6 | 47.6 | 26.1 | 225 | 65 | 14 | 62.8 | 60.6 | 55.3 |
| 2.5 | 1 | 21.5 | 124.5 | 99.6 | 480 | 24 | 8 | 50.5 | 50.5 | 53.0 |
| 1.3 | 0.4 | 21.5 | 27.8 | 19.4 | 29 | 133 | | | | |
| 1.5 | 2 | 22.8 | 64.8 | 42.5 | 184 | 53 | | | | |
| Average | | 21.0 | 65.7 | 38.9 | | | | 61.4 | 53.3 | 55.1 |
| Increase in per cent of average $\beta = 213$ | | | | | | Recovery in per cent of average $\beta = 60$ | | | | |

¹ Urethane anaesthesia.

creased to 77.6 β units (at 2), an increase of 219 per cent. Eighteen minutes later it was again determined and found to be 77.6 β units (at 3). Adrenalin 0.5 c.c. (1:100,000) was then injected intravenously, and six minutes later the threshold (at 4) was found to be 43.2 β units, a recovery of 64 per cent. After 15 minutes' rest the threshold (at 5) was 39.8 β units, and 10 minutes later, after an injection of 5 c.c. of curare, the threshold (at 6) was 64 β units, an increase of 60 per cent.

Since fatigue increases the threshold of a denervated muscle it was interesting to note whether or not it would have an effect upon the threshold of a curarized muscle.¹

Six experiments were performed. The average β after curare was 60.5. This was increased by fatigue to an average β of 370.6, an increase of 512 per cent. Five minutes or less after an injection of 0.1 to 3.5 c.c. of adrenalin (1:100,000) this threshold was decreased to 176 β units, a recovery of 62 per cent.

DOES CURARE OR ADRENALIN AFFECT THE THRESHOLD OF THE NORMAL UNFATIGUED DENERVATED MUSCLE?

In Table I (II) the average threshold of the denervated muscle, for six experiments, was 61.4 β units. After an injection of curare which completely immobilized the animal the average threshold was 53.3 β units and after an injection of adrenalin the threshold was 55.1 β units. From this table and the broken line in Fig. 2 it is evident that neither curare nor adrenalin affects unfatigued muscles in which the nerve endings are degenerated.

¹ GRUBER: this journal, 1913, xxxii, p. 444; *Ibid.*, 1914, xxxiii, p. 345.

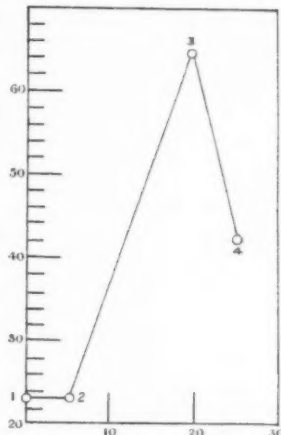


FIGURE 1.—A curve plotted from the data of one experiment. Urethane anaesthesia. The time interval in minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. 1. Normal threshold stimulus 22.8 β units. 2. Threshold after 5 minutes' rest 22.8. 3. The threshold 16 minutes after an injection of 2.5 c.c. of curare, 64.9 β units. 4. The threshold 5 minutes after an injection of 2 c.c. of adrenalin (1:100,000), 42.5 β units.

The conditions for testing the denervated muscle were the same as those for the right tibialis anticus, the results of which are shown in the continuous line in the same figure. The slight variations in the curve of the denervated muscle are amply within the limits of error. That there is such marked similarity between the threshold stimuli of the denervated and curarized muscles

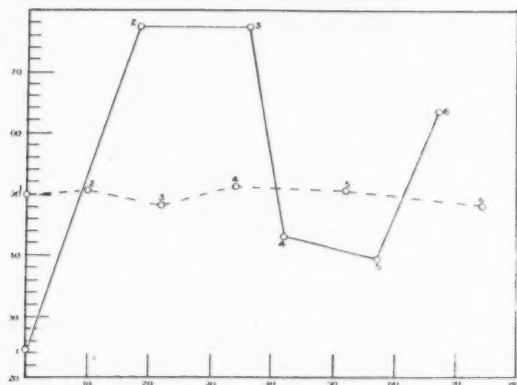


FIGURE 2. — A curve plotted from the data of one experiment performed on a decerebrate cat. The time interval in minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the normal right tibialis anticus muscle, the broken line that of the denervated left tibialis anticus (left peroneus communis nerve cut 7 days previous).

The normal muscle: 1. The normal threshold, 24.25 β units. 2. 18 minutes after an injection of 3 c.c. of a 3 per cent solution of curare (animal totally paralyzed) 77.6 β units. 3. After 18 minutes' rest 77.6 β units. 4. The threshold 6 minutes after an injection of 0.5 c.c. of adrenalin (1:100,000), 43.15 β units. 5. After a rest of 15 minutes 39.8 β units. 6. The threshold 10 minutes after an injection of 5 c.c. of a 3 per cent solution of curare 64 β units.

In the denervated muscle: 1. Normal threshold 50 β units. 2. Ten minutes after curare was injected 50.8 β units. 3. 12 minutes later 48.4 β units. 4. 12 minutes later 51.6 β units. 5. 18 minutes after an injection of 0.5 c.c. of adrenalin (1:100,000), 50.8 β units. 6. 22 minutes later or 10 minutes after an injection of 5 c.c. of curare, 48.4 β units.

indicates that seven days are sufficient for degeneration of the severed nerves. The average threshold stimulus of the 14 denervated muscles which were inexcitable on strong faradic stimulation of their cut nerves, was 62.5 β units and that of the curarized animals, in which there was complete immobility, was 63.5 β units. See Table II.

TABLE II

The Threshold Stimulus of the Tibialis Anticus Muscle in Decerebrate and Urethanized Cats. Measurements taken by the Martin Method. (I) Peroneus Communis Nerve Degenerated. (II) Curare Paralysis.

| Date of the experiment | Number of days nerve cut | Threshold in β units | Date of the experiment | Quantity of curare in c.c. | Threshold in β units |
|------------------------|--------------------------|----------------------------|------------------------|----------------------------|----------------------------|
| July 7 | 6 | 119.2 | June 25 | 2 | 42.6 |
| ¹ July 8 | 7 | 83.5 | ¹ June 26 | 3 | 38.5 |
| July 22 | 7 | 52.5 | ¹ June 26 | 4 | 80.4 |
| July 23 | 8 | 93.2 | June 28 | 1.5 | 55.2 |
| July 31 | 7 | 50.0 | June 28 | 2 | 73.1 |
| Aug. 1 | 8 | 59.6 | ¹ June 30 | 2.5 | 74.8 |
| Aug. 7 | 14 | 79.4 | ¹ June 30 | 3 | 27.8 |
| ¹ Aug. 18 | 8 | 50.5 | ¹ June 30 | 1.5 | 64.9 |
| ¹ Aug. 26 | 7 | 42.6 | July 22 | 4.5 | 70 |
| ¹ Sept. 3 | 15 | 100.1 | July 23 | 4 | 72 |
| ¹ Sept. 5 | 9 | 21.5 | July 31 | 3 | 77.6 |
| ¹ Sept. 8 | 12 | 36.4 | Aug. 1 | 3 | 41.2 |
| ¹ Sept. 20 | 14 | 53.4 | Aug. 7 | 2.5 | 47.6 |
| ¹ Sept. 22 | 16 | 32.9 | Aug. 18 | 2.5 | 124.5 |
| Average | | 62.5 | Average | | 63.5 |

¹ Urethane anaesthesia.

The increase in the normal threshold by curare is probably due to the elimination of the nervous elements. When platinum needle electrodes are thrust into a muscle and the muscle is stimulated electrically, both nerve and muscle tissue are affected. After an injection of curare in sufficient amounts, the irritability of the nerve tissue is eliminated and only muscle tissue is stimulated. The threshold is thus increased. That this is due solely to abolishing nervous influence is shown by the close correspondence

of the average thresholds of curarized muscle and of denervated muscle. See Table II.

Probably curare acts upon a different substance than that upon which fatigue acts. Fatigue increases the threshold of a muscle whether denervated by nerve degeneration, or curare, whereas curare affects only the threshold of a muscle in which the nerve endings are normal.

That adrenalin decreases the threshold of the curarized tibialis anticus has been demonstrated, but the manner in which it exerts this antagonistic action is quite obscure, since the point of action of adrenalin is not definitely known.

SUMMARY

1. Curare increases the threshold of the normal muscle but not the threshold of a muscle in which the nerve endings have degenerated.
2. Adrenalin is an antagonist to curare and decreases, in five minutes or less, the curare threshold, in some cases to normal.
3. Fatigue increases the threshold of a curarized muscle, and adrenalin antagonizes this fatigue.
4. The substance upon which curare acts is probably different from that upon which fatigue acts. It either degenerates upon nerve degeneration, is transformed by muscle atrophy or is inexcitable to electrical stimuli.

VARIATIONS IN THE SENSORY THRESHOLD FOR FARADIC STIMULATION IN NORMAL HUMAN SUBJECTS

III. THE INFLUENCE OF GENERAL FATIGUE

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IN connection with a series of studies being carried on in this laboratory of variations in electro-cutaneous sensibility in normal human beings we have made some observations which seem to show that a state of general fatigue, incident to the daily routine and cumulative from day to day, manifests itself as a progressive general rise in the value of the threshold stimulus. This, in turn, signifies a progressive lowering of sensitiveness and, according to the view of Grabfield and Martin,¹ a diminishing tone of the nervous mechanism as a whole. Our observations indicate further that a pronounced break in the routine may bring about a restoration of sensitiveness to a high point, from which it sinks again as the routine proceeds.

The subjects of our experiments were nine first-year medical students, young adult males in good health. The observations were made in term time. The subjects, therefore, were following a routine which was necessarily regular and similar during six days of each week, made so by the pressure of the school exercises. The routine was interrupted weekly by the Sunday recess, an interval occupied variously by the subjects, but in no case in precisely the manner of the week days.

The sensory thresholds were determined in β units² according

¹ GRABFIELD and MARTIN: this journal, 1913, xxxi, p. 308.

² MARTIN: The measurement of induction shocks, New York, 1912, p. 76.

to the method described by Grabfield and Martin.¹ Daily readings were made on all the subjects except two between 12.30 P.M. and 1.30 P.M. This period, according to Grabfield and Martin (*loc. cit.*, p. 306), is specially satisfactory for taking readings, since then the sensory threshold is usually at about the position of the average for the day. Two of the subjects were being observed daily at 9.00 A.M. in connection with a special problem. The results obtained from them are included with the others without any attempt at correction for diurnal variation.

In Table I our observations are compiled for convenient reference. To facilitate comparison the data for each day of the week are grouped together. Four vertical columns are devoted to each subject; the first contains the observed thresholds in β units; the second the values of reciprocal $\beta \times 10^4$, used in these studies as indices of irritability²; the third the values for irritability reduced to a percentage basis³; the fourth the average percentage irritability for each week day. For such studies as this the use of relative or percentage irritabilities, rather than actual irritabilities, is instructive, since the percentage figures not only reveal the extent of departure of each subject from his own average irritability, but also allow direct comparisons between various subjects, whether they happen to have a high or a low general level of sensitiveness.

The data on which we base the conclusion set forth at the beginning of the paper appear in the table in the fourth column under each subject, where the percentage irritabilities for each week day are averaged. These average figures show a well-marked tendency for the irritability to diminish from day to day as the week progresses. There are, as must be expected, departures from this tendency in individual cases, but on the whole, the decline in irritability seems too pronounced to be accidental. Furthermore, the observations were spread over a sufficient number of weeks to avoid the likelihood that irritability changes, interpreted as due to general fatigue, were in reality the result of meteorological or other special conditions.

¹ GRABFIELD and MARTIN: *Loc. cit.*, p. 303.

² GRABFIELD and MARTIN: *Loc. cit.*, p. 306.

³ *Ibid.*, p. 307.

TABLE I

DAILY VARIATIONS IN IRRITABILITY, GROUPED ACCORDING TO DAYS OF THE WEEK

*Subject O.**Subject B.*

| Date | β | Recip. β $\times 10^4$ | $\frac{c}{c}$ rec. β | Daily av. | β | Recip. β $\times 10^4$ | $\frac{c}{c}$ rec. β | Daily av. |
|----------|---------|---------------------------------|----------------------------|--------------|---------|---------------------------------|----------------------------|--------------|
| 1913 | | | | | | | | |
| Mar. 17, | | | | | 69.1 | 145 | 99 | |
| 24 | | | | | 77.6 | 129 | 88 | |
| 31 | 76.3 | 131 | 116 | | | | | |
| Apr. 7 | 78.8 | 127 | 112 | | | | | |
| 14 | | | | | | | | |
| 21 | 88.1 | 114 | 101 | 110 | 47.1 | 212 | 144 | 107 |
| May 19 | | | | | | | | |
| Mar. 18 | | | | | 65 | 154 | 105 | 105 |
| 25 | | | | | | | | |
| Apr. 1 | 81.4 | 123 | 109 | 109 | | | | |
| 15 | | | | | | | | |
| May 13 | | | | | | | | |
| Mar. 19 | | | | | 72.3 | 138 | 94 | |
| 26 | | | | | | | | |
| Apr. 2 | 83.6 | 120 | 106 | 106 | | | | |
| 9 | | | | | | | | |
| 16 | | | | | 65.5 | 153 | 104 | 99 |
| May 14 | | | | | | | | |
| Mar. 13 | | | | | | | | |
| 20 | | | | | 88.2 | 113 | 77 | |
| 27 | | | | | | | | |
| Apr. 3 | 100.8 | 99 | 88 | | | | | |
| 10 | 95.7 | 105 | 93 | 90 | 60.4 | 166 | 113 | 95 |
| May 15 | | | | | | | | |
| 7 | | | | | 71.1 | 141 | 96 | |
| Mar. 14 | | | | | | | | |
| 21 | | | | | 72.4 | 138 | 94 | |
| 28 | | | | | | | | |
| Apr. 4 | 98 | 102 | 90 | 90 | | | | |
| 11 | | | | | 68.9 | 145 | 99 | 96 |
| 18 | | | | | | | | |
| May 16 | | | | | | | | |
| Mar. 15 | | | | | | | | |
| 22 | | | | | 77.9 | 128 | 87 | 87 |
| 29 | 94.1 | 106 | 94 | | | | | |
| Apr. 5 | 101.2 | 99 | 98 | 91 | | | | |

TABLE I. (Continued)

*Subject L.**Subject Wt.**Subject H.*

| Date | β | Recip. $\beta \times 10^4$ | % rec. β | Daily av. | β | Recip. $\beta \times 10^4$ | % rec. β | Daily av. | β | Recip. $\beta \times 10^4$ | % rec. β | Daily av. |
|---------|---------|-------------------------------|-------------------|--------------|---------|-------------------------------|-------------------|--------------|---------|-------------------------------|-------------------|--------------|
| 1913 | | | | | | | | | | | | |
| Mar. 17 | | | | | | | | | | | | |
| 24 | | | | | | | | | | | | |
| 31 | 93.2 | 107 | 86 | | 53.7 | 188 | 146 | | 80 | 125 | 93 | |
| Apr. 7 | 55 | 182 | 147 | | 90.2 | 111 | 86 | 116 | 68 | 147 | 109 | |
| 14 | | | | | | | | | | | | |
| 21 | 62.2 | 161 | 130 | 121 | | | | | 75.3 | 133 | 99 | 100 |
| May 19 | | | | | | | | | | | | |
| Mar. 18 | | | | | | | | | | | | |
| 25 | | | | | | | | | | | | |
| Apr. 1 | 77.5 | 129 | 104 | 104 | 78 | 128 | 99 | 99 | 72.3 | 138 | 102 | 102 |
| 15 | | | | | | | | | | | | |
| May 13 | | | | | | | | | | | | |
| Mar. 19 | | | | | | | | | | | | |
| 26 | | | | | | | | | 69.8 | 143 | 106 | |
| Apr. 2 | 93.3 | 107 | 86 | 86 | 71.8 | 139 | 108 | 108 | 66.1 | 151 | 112 | 109 |
| 9 | | | | | | | | | | | | |
| 16 | | | | | | | | | | | | |
| May 14 | | | | | | | | | | | | |
| Mar. 13 | | | | | | | | | | | | |
| 20 | | | | | | | | | | | | |
| 27 | | | | | | | | | | | | |
| Apr. 3 | 92.2 | 108 | 87 | | 78.8 | 127 | 98 | 98 | 64.5 | 155 | 115 | |
| 10 | 65.2 | 153 | 123 | 105 | | | | | 66.1 | 151 | 112 | 113 |
| May 15 | | | | | | | | | | | | |
| 7 | | | | | | | | | | | | |
| Mar. 14 | | | | | | | | | | | | |
| 21 | | | | | | | | | | | | |
| 28 | | | | | 79.6 | 126 | 98 | | 80.6 | 124 | 92 | |
| Apr. 4 | 108.3 | 92 | 74 | | 92.5 | 108 | 84 | 91 | 84.7 | 118 | 88 | 90 |
| 11 | 89.7 | 111 | 90 | 82 | | | | | | | | |
| 18 | | | | | | | | | | | | |
| May 16 | | | | | | | | | | | | |
| Mar. 15 | | | | | | | | | | | | |
| 22 | | | | | | | | | | | | |
| 29 | 86.8 | 115 | 93 | | 77.1 | 130 | 101 | | 96 | 104 | 77 | |
| April 5 | 99.3 | 101 | 81 | 87 | 96.6 | 103 | 80 | 90 | 88.5 | 113 | 84 | 80 |

TABLE I. (Continued)

Subject Wb.

Subject Wl.

| Date | β | Recip. β $\times 10^4$ | % rec. β | Daily av. | β | Recip. β $\times 10^4$ | % rec. β | Daily av. |
|---------|---------|---------------------------------|----------------|--------------|---------|---------------------------------|----------------|--------------|
| 1913 | | | | | | | | |
| Mar. 17 | | | | | 94.9 | 105 | 95 | |
| 24 | 87 | 115 | 100 | | | | | |
| 31 | 65.4 | 153 | 133 | | 77.6 | 129 | 116 | |
| Apr. 7 | | | | | 111.5 | 90 | 81 | |
| 14 | 114 | 88 | 76 | | | | | |
| 21 | 60.9 | 164 | 142 | 113 | 79.2 | 126 | 113 | 101 |
| May 19 | | | | | | | | |
| Mar. 18 | | | | | 84.8 | 118 | 106 | |
| 25 | 100.5 | 100 | 87 | | 92.6 | 108 | 97 | |
| Apr. 1 | | | | | 73 | 137 | 123 | 109 |
| 15 | 88.3 | 113 | 98 | 92 | | | | |
| May 13 | | | | | | | | |
| Mar. 19 | | | | | 64.9 | 150 | 135 | |
| 26 | 94.6 | 106 | 92 | | 94.8 | 105 | 95 | |
| Apr. 2 | 71.4 | 140 | 122 | 107 | 95.6 | 104 | 94 | 108 |
| 9 | | | | | | | | |
| 16 | | | | | | | | |
| May 14 | | | | | | | | |
| Mar. 13 | | | | | 127.5 | 78 | 70 | |
| 20 | | | | | 109 | 92 | 83 | |
| 27 | 100.9 | 99 | 86 | | 63.1 | 158 | 142 | |
| Apr. 3 | 98 | 102 | 89 | 87 | 80.5 | 124 | 112 | |
| 10 | | | | | 92.1 | 108 | 97 | 101 |
| May 15 | | | | | | | | |
| Mar. 7 | | | | | | | | |
| 14 | | | | | 111.5 | 90 | 81 | |
| 21 | | | | | 100 | 100 | 90 | |
| 28 | 107.5 | 93 | 81 | | 95.6 | 104 | 94 | |
| Apr. 4 | 104.1 | 96 | 83 | | 93.4 | 107 | 96 | 90 |
| 11 | 64.3 | 155 | 135 | 100 | | | | |
| 18 | | | | | | | | |
| May 16 | | | | | | | | |
| Mar. 15 | | | | | 117.8 | 85 | 77 | |
| 22 | | | | | | | | |
| 29 | 115.7 | 86 | 75 | | 93.1 | 107 | 96 | 86 |
| Apr. 5 | 87.6 | 114 | 99 | 87 | | | | |
| 19 | | | | | | | | |
| May 17 | | | | | | | | |

TABLE I. (Continued)

*Subject G.**Subject McG.*

| Date | β | Recip. β $\times 10^4$ | % rec. β | Daily av. | β | Recip. β $\times 10^4$ | % rec. β | Daily av. |
|---------|---------|---------------------------------|----------------|--------------|---------|---------------------------------|----------------|--------------|
| 1913 | | | | | | | | |
| Mar. 17 | | | | | | | | |
| 24 | 144 | 70 | 92 | | 51 | 196 | 105 | |
| 31 | | | | | | | | |
| Apr. 7 | | | | | | | | |
| 14 | 131 | 76 | 100 | 96 | 51 | 196 | 105 | |
| 21 | | | | | | | | |
| May 19 | | | | | 65 | 154 | 83 | 98 |
| Mar. 18 | | | | | | | | |
| 25 | 119 | 84 | 110 | | 49 | 204 | 110 | |
| Apr. 1 | 140 | 71 | 93 | | | | | |
| 15 | 141 | 71 | 93 | 99 | 47 | 213 | 114 | |
| May 13 | | | | | 57 | 175 | 94 | 106 |
| Mar. 19 | | | | | | | | |
| 26 | 122 | 82 | 108 | | | | | |
| Apr. 2 | 123 | 81 | 107 | | | | | |
| 9 | | | | | | | | |
| 16 | 133 | 75 | 99 | 105 | 45 | 222 | 119 | |
| May 14 | | | | | 62 | 161 | 87 | 103 |
| Mar. 13 | | | | | | | | |
| 20 | | | | | 44 | 227 | 122 | |
| 27 | | | | | | | | |
| Apr. 3 | 132 | 76 | 100 | 100 | | | | |
| 10 | | | | | | | | |
| May 15 | | | | | 55 | 182 | 98 | 110 |
| Mar. 7 | | | | | | | | |
| 14 | | | | | | | | |
| 21 | 129 | 78 | 103 | | 50 | 200 | 107 | |
| 28 | | | | | 68 | 147 | 79 | |
| Apr. 4 | | | | | | | | |
| 11 | | | | | | | | |
| 18 | 108 | 93 | 122 | 112 | 42 | 238 | 128 | |
| May 16 | | | | | 66 | 151 | 81 | 99 |
| Mar. 15 | | | | | | | | |
| 22 | 142 | 70 | 92 | | 50 | 200 | 107 | |
| 29 | | | | | | | | |
| Apr. 5 | 145 | 69 | 91 | | 56 | 179 | 96 | |
| 19 | 144 | 69 | 91 | 91 | 69 | 145 | 78 | |
| May 17 | | | | | 64 | 156 | 84 | 91 |

As a means of summarizing our observations the curve shown in Fig. 1 is presented. All the percentage irritabilities for each week day as given in Table I were averaged, and the values thus obtained were plotted against the days of the week with which they correspond. The curve pictures clearly a progressive diminution in sensitiveness which we believe to be characteristic of the human nervous mechanism under such conditions of general fatigue as result from a rather pressing routine.

Although our conclusion is based upon averages, it is supported by direct comparison of the irritabilities of Saturdays and the Mondays following. We have examined 19 such pairs of observations upon the nine subjects of this study and upon two additional subjects. These enable us to compare with the results obtained by the study of averages, the effects on individual cases of the interruption of routine. Of our nineteen observations, twelve showed greater irritability on Monday than on the preceding Saturday; three showed a diminished irritability; and four showed no change. The four cases of unchanged irritability all occurred in three subjects. Of the three cases of lowered irritability two occurred in subjects who at other week ends showed marked increase of sensitiveness. The other case was of a subject upon whom the observations were discontinued before a second week end arrived. The increase of irritability in the twelve cases that showed it, ranged from 7.5 per cent to 82 per cent, averaging 30 per cent; the decrease in the three cases that showed that change, ranged between 7.5 per cent and 15.6 per cent, averaging only 10 per cent.

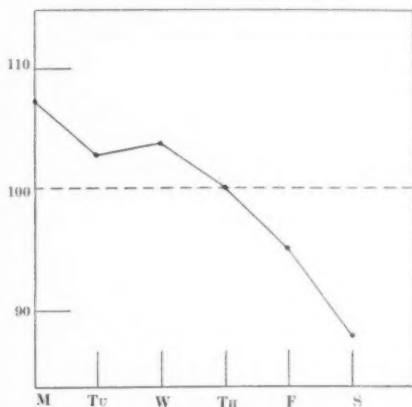


FIGURE 1. Curve of percentage irritabilities showing the general decline in irritability during the week.

In comparison with these observations, and for further assur-

ance that the effects observed are actually associated with the conditions of routine, as we have assumed, we have studied in sixteen cases the irritability on two successive days in the middle of the week. Of these sixteen, eight showed diminished sensitiveness, six increased sensitiveness, and two no change. An interesting fact is that the eight subjects whose irritability change was in the general direction called for by our assumption had an average extent of change of 23.5 per cent, while the six whose irritability change was in the opposite direction had an average extent of change of only 14.9 per cent.

When we consider how many unexplained factors undoubtedly

have influence in determining the threshold of sensitiveness from time to time the general relationship we have reported between irritability and routine seems to us undoubtedly significant.

As illustrating the way in which the sensitiveness may follow the routine over a considerable period we reproduce in Fig. 2 the curve of irritability of a single subject, O., from March 29 to April 10, 1913. This subject is a man of very regular habits, and therefore highly favorable for such a

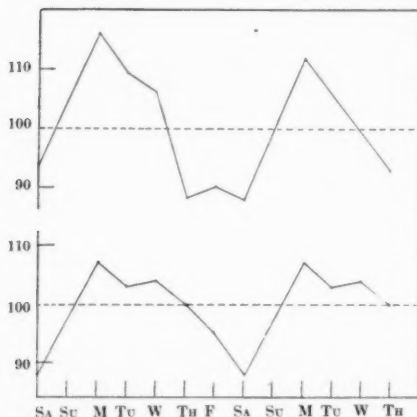


FIGURE 2. Upper curve, the variations in irritability from day to day of a single subject; lower curve, the curve of Figure 1 for general irritability extended to include the same period as does the upper one.

study as this one. For comparison our curve of average daily irritability (Fig. 1) is set alongside the other, extended to make it cover the same period.

SUMMARY

Daily observations for several weeks on nine subjects, all following a regular and somewhat pressing routine, show that at the beginning of the week the irritability tends to be high, that from then till the end of the week there is a fairly continuous

decline in irritability, as judged by the sensory threshold, and that following the interruption of the routine by the intervention of Sunday the irritability returns to its original high point.

This is interpreted as a result of general fatigue incident on routine and restoration of nervous tone following a marked interruption therein.

TWO TYPES OF REFLEX FALL OF BLOOD PRESSURE

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CHANGES in arterial pressure may be caused by changes in the total volume of the blood, by variations in the output from the left ventricle, or by changes in the peripheral resistance. Alterations of the last-named condition may be due to local influences brought to bear upon the musculature, as in the effect of adrenalin, or to vasomotor mediation. If we limit our attention to the vasomotor factors we recognize that a dilation with lowering of resistance to the blood-stream may be occasioned by a lowering of the tonic activity of the vasoconstrictor centre or, at another time, by the intervention of vasodilator impulses. Presumably the widest possible opening of the vascular channels will be secured when vasoconstrictor tone is abolished and the dilators are universally stimulated.

With regard to the afferent side of the mechanism by which the calibre of the small blood-vessels is changed we have had a very clear conception of the several possibilities ever since their presentation by Hunt¹ in 1895. A fall of pressure, reflexly brought about, may be the result of reduced tonic activity on the part of the vasoconstrictor centre; in this case the afferent fibres concerned are said to have a depressor effect. Such a fall may be the expression of dilators coming into play; in this case it is appropriate to call the afferent fibres excito-dilators. Excito-dilator reflexes need not be assumed to involve a localized vasodilator centre, no such anatomical feature being known. Evidently, a given sensory nerve may contain both depressor and excito-dilator fibres, or the same fibres may make central connections such as to mediate both reactions.

¹ HUNT: *Journal of physiology*, 1895, xviii, p. 381.

The best known example of a nerve which can be relied upon to produce a reduction of blood-pressure when its central end is stimulated is found in the group of afferent fibres commonly called the Depressor.¹ This appears in the rabbit and some other animals as a strand accompanying the vagus. It is assumed to be represented in other cases by a set of fibres within the vagus trunk. These fibres have been said to originate in the wall of the aorta and to be stimulated by the distension of that vessel near its root. Thus a rise of aortic pressure tends to secure a compensatory adjustment and to be promptly abated.

The Depressor nerve, or the depressor fibres, have been believed to effect a lowering of arterial tension partly through reflex inhibition of the heart but more extensively in the animals usually chosen for experiment by suppressing the tonic action of the vasoconstrictor centre. If the reaction were confined to this mode of operation the name Depressor (by which depressor par excellence seems to be implied) would be fully justified. Sherrington² has with great ingenuity brought this central action into the class of reciprocal innervation. He points out that the circular muscle elements in the blood-vessels are the true antagonists of the cardiac elements and that it is to be expected that an increased action of the heart will be attended by an inhibition of the vascular musculature, just as the contraction of a flexor is accompanied by the inhibition of the corresponding extensor.

But the actual working of the Depressor is not limited to the inhibition of existing vasoconstrictor tone. There is an enlisting of vasodilators in the response and a certain share of the loss of pressure is to be referred to this action. Bayliss³ was led to believe this even before the work of Hunt mentioned above had been published. In 1893 he expressed his opinion that one can discover traces of the dilator effect in the presence of the true depressor phenomenon. Much later⁴ he studied the submaxil-

¹ LUDWIG and CYON: *Berichte d. k. Gesellschaft, math. phys. Classe.*, Leipzig, 1866, p. 307.

² SHERRINGTON: *The integrative action of the nervous system*, Scribners, New York, 1906, p. 99.

³ BAYLISS: *Journal of physiology*, 1893, xiv, p. 314.

⁴ BAYLISS: *Journal of physiology*, 1908, xxxvii, p. 264. Also FOFANOW and TSCHALLUSOW: *Archiv für die gesammte Physiologie*, 1913, cli, p. 543.

lary gland in this connection with clear and interesting results. The constrictor supply of this gland may be cut off by severing the cervical sympathetic. After this has been done, stimulation of the depressor still accelerates the flow from the vein of the gland, a fact which must be accounted for on the assumption of a positive excitation of the dilator fibres in the chorda tympani. The converse experiment—cutting the chorda and obtaining a real depressor reaction from the gland—is also successful.

Bayliss noted that the type of pressure reduction which he referred to the dilators was moderate in degree and not lasting. The profound lowering seen when the stimulation of the Depressor is adequate may be continued for a long time with little or no exhibition of a tendency toward a recovery of normal pressure. Bayliss suggested that the transient action of the dilator mechanism might be held to indicate central fatigue and that fatigue is something which we expect to see in connection with an excitatory process. An inhibitory process, on the other hand, might not entail any fatigue because of its negative character; it certainly should not on the Gaskell conception of anabolic processes in the cells involved. At any rate, the main effect of depressor stimulation is one which may be maintained without flagging for as long as 17 minutes.

The present paper is to report the results of an attempt to bring the Martin method for the physiological calibration of induction shocks¹ to bear upon the analysis of the depressor reaction. These experiments have been upon cats. In this animal a separate Depressor is said to be frequently found. Our experience does not confirm such a statement although the number of animals observed has been small. Out of some fifteen cats we have seen in two cases only, a slender nerve alongside the vagus which would have been taken for a Depressor on anatomical grounds. In both these cases stimulation of the nerve in question failed to give the typical depressor reaction and this was found to be obtainable by stimulating the main trunk of the vagus. We have once seen the complete failure of the usual effect when

¹ MARTIN: *The measurement of induction shocks*, Wiley, New York, 1912.

the central end of the vagus was excited and in this instance the power was found to reside in the nerve of the opposite side.

Our procedure has been to anaesthetize, sometimes with ether and at other times with urethane. Tracheotomy has then been performed and both the vagi have been cut. Stimulation has been by means of a Sherrington electrode connected with a calibrated induction coil. Break shocks have been given by means of a mechanical, motor-driven interrupter at rates between 8 and 15 per second. The blood pressure has been taken in most cases from the femoral artery. It is better to use this vessel than the carotid because if the latter is chosen there is danger of wetting the nerve with the fluid used to retard coagulation, in this research a strong solution of sodium carbonate.

The strength of the stimulation employed was deduced from the position of the secondary coil and the amperage of the primary current. Our figures are therefore in the Z-units of Martin¹ and are not corrected for variations of external resistance. Under this system one reading can be fairly compared with another so long as the electrode remains in one position; the readings cease to be accurately comparable otherwise, and yet their range from one experiment to another continues to have a general value.

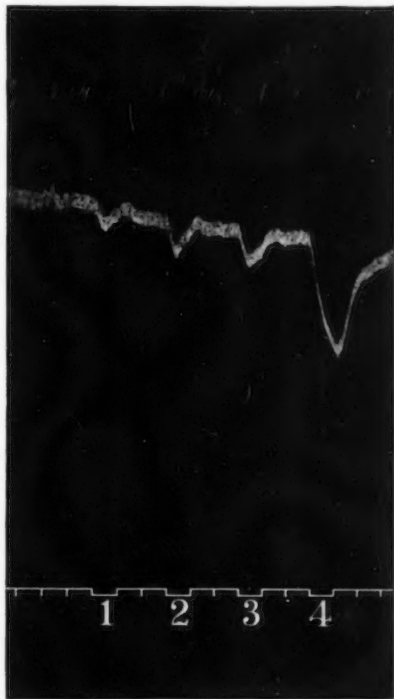


FIGURE 1. — Showing the slight increase of effect upon the blood pressure following stimuli rated as 22, 35, and 60Z (1, 2, 3 in the record) and the profound effect of the stimulus of 127Z (4), this being above the Depressor threshold.

¹ MARTIN: *loc. cit.*, p. 73.

It is to be remembered that we are dealing with a series of nerves which vary in size and physical condition only within rather narrow limits.

A series of typical results may now be described. If we begin with stimuli too weak to affect the blood pressure and proceed to apply stronger and stronger ones we shall presently obtain a response which is recorded as a transient lowering of pressure. This is the reaction interpreted by Bayliss as a reflex through the dilators. There is usually a partial recovery within the period of 30 seconds during which we ordinarily continue to stimulate. With gradually increasing intensity of stimulation through a considerable range this "mild" reaction is repeated with but little augmentation. Often there is an "all or none" character about it which is quite suggestive.

Since we are making use of a mixed nerve and not a pure Depressor such as can be found in the rabbit, there is, of course, the possibility of reflexes from the skeletal muscles, particularly those concerned in the breathing movements. But as a matter of fact these disturbances have very seldom become noticeable. Nearing a certain level we begin to see hints of the change from the mild to the profound depression of the blood pressure and when the threshold is cleared the effect quickly becomes maximal. The fall of pressure is now a matter of 25 per cent or more and there is no rebound within the stimulation period of 30 seconds. It is to be noted that the cutting of the other vagus has subtracted from the possible depression that fraction which could have been produced in the normal animal through reflex inhibition of the heart. A further increase of stimulation above that giving the typical depressor effect adds but little to its magnitude.

Here we have very distinctly the appearance of two thresholds. The lower of these is measured by the strength of stimulation necessary to secure the "mild" or supposed excito-dilator response. How wide is the interval between this and the higher one, assumed to be the threshold for inhibition of the vaso-constrictor centre, will be made plain by the following table. The attempt to assign precise values to these thresholds does not lead to satisfactory results. The full depressor reaction does not appear all at once when the record first shows a departure

from the excito-dilator curve; there is a relatively narrow range within which the influence of changing stimulation is a graded one. One reason why the thresholds cannot be very sharply defined is found in the shifting due to modified conditions accompanying repeated trials.

Our chief results may be conveniently grouped as below:

- 54 trials in which the average stimulus was 10Z gave an average drop of 6 per cent.
- 59 trials in which the average stimulus was 70Z gave an average drop of 8 per cent.
- 28 trials in which the average stimulus was 175Z gave an average drop of 8.5 per cent.
- 54 trials in which the average stimulus was 250Z gave an average drop of 27 per cent.

The entrance of the second, or profound, effect is evident. If we were to add a fifth group comprising the stimuli which were manifestly supra-maximal, the average pressure reduction would still be in the vicinity of 27 per cent.

Attention may again be called to the approximately "all or none" character of the mild or assumed vasodilator reaction. It appears in the tabulation above that an increase of strength of stimulus from 10Z to 175Z, that is, a 17-fold multiplication, makes the sagging of the blood-pressure only slightly more pronounced. We could cite one series after another, chosen from the records averaged in our summary, in which the weak stimuli were fully as efficient as those many times stronger. This is so striking as to make it desirable to have a comparison between these vagal reflexes and those obtainable from other nerves. We are able to introduce the desired figures for the sciatic, the saphenous, and for certain branches of the brachial plexus.

The application of stimuli to the central end of the sciatic can be depended upon to cause a moderate lowering of pressure so long as the stimuli are below a certain intensity. Using this nerve we passed on one occasion, by many gradations, from a stimulation strength of 11Z to 45Z and obtained with the weakest stimulus a drop of 8.5 per cent and with the strongest a fall of 8.3 per cent. The intermediate values were all between 5.4 and

8.9 per cent. In another experiment the change of pressure remained between 10 and 11 per cent while the stimulation was shifted from 35 to 86Z. Again, the effect varied only between 10.6 and 11.1 while the stimulation was changed in strength from 41 to 145Z.

When the saphenous nerve has been under observation it has been the general experience that very strong stimuli have given no greater reduction of pressure than could be secured by the employment of others much weaker. This is a small nerve and it is doubtless more subject to injury than are the others we have used. For this reason somewhat less dependence is to be placed upon the quantitative findings based upon its investigation. But when due allowances are made the results still appear to be significant. For example, in a series of six trials in which the weakest stimulus was 3.25Z and the strongest 360Z the effect of the first was a fall of 8.1 and of the last 8.2 per cent. The intermediate stimulations gave magnitudes varying between 2.9 and 9.2 per cent, a wide fluctuation but entirely unrelated to the stimulation gradient. In another experiment a descending series of five trials gave the following results: for 60Z a drop of 9.6 per cent, for 11Z a drop of 9.1 per cent. The three intermediate figures for the pressure change are 10.7, 8.9, and 10.9 per cent.

The nerves of the fore-limb are probably more reliable for our purpose. From these we have obtained such results as the following: in one instance a stimulus rated as 5Z produced a fall of 9.1 per cent, 11Z gave 9.2 per cent, 22Z gave 7.0 per cent, and 360Z gave 11.6 per cent. In another protocol we find that 5Z gave a fall of 5.3 per cent, 11Z gave 4.0 per cent, and 60Z 4.1 per cent.

Reviewing our data we are not disposed to claim that the excito-dilator reaction has an all or none character in precisely the same sense that the heart muscle has that property. When we use this expression with reference to the heart we mean that the least stimulus capable of evoking any response causes a full-sized contraction. In this case we believe rather that the excito-dilator reaction is a graded one from its threshold through a limited range of stimulation, but that a maximal effect is

soon attained and that the stronger stimuli are then supra-maximal.

Martin and Lacey¹ have recently reported that with afferent nerves other than the vagus a depressor reaction is exchanged for a pressor effect when the stimulation is carried above a threshold of reversal which they have found to be near 280Z. The figures we have cited for the vagus show that our second type of reaction is superimposed upon the first when the strength of the shocks applied is of a roughly similar order. (The difference between the position of the secondary coil for a stimulus of 250Z and that necessary to give 300Z is but a few millimetres.) The obvious suggestion is that the threshold for the inhibition of the vasoconstrictor centre is the same as for its excitation. In the solitary case in which we could not elicit the depressor property from the vagus we found that this nerve like others produced pressor reactions when strongly stimulated. The reversal occurred in the vicinity of a stimulation strength of 400Z.

Our attention was called by Doctor Cannon to the possibility that the mild type of depression might be due to a reflexly induced discharge of adrenalin of the order of magnitude which Cannon and Lyman² found to cause vasodilation. It seemed to us that the response was rather too prompt to be accounted for in this way, but we made a precautionary experiment in which the adrenal bodies were excluded from the circulation. We found that we could still obtain the familiar reduction of 5 to 10 per cent on applying weak stimuli to the vagus.

¹ MARTIN and LACEY: this journal, 1914, xxxiii, p. 212.

² CANNON and LYMAN: this journal, 1913, xxxi, p. 376.

THE INFLUENCE OF FOOD, POSTURE, AND OTHER FACTORS ON THE ALVEOLAR CARBON DIOXIDE TENSION IN MAN

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INTRODUCTION

THE tension of CO_2 in the alveolar air, representing the CO_2 tension in the arterial blood, was shown by Haldane and Priestley¹ to be the normal regulator of respiration. It was further shown by these authors and later more extensively by Fitzgerald and Haldane² that the alveolar CO_2 tension of the same individual was practically always the same, although individuals differed markedly from each other as to their normal CO_2 tension. But under abnormal or unusual conditions the CO_2 tension has been found to vary from the normal. Especially is this the case when there is an acidosis, or increase of acid in the blood; in such conditions there is a lower alveolar CO_2 tension. This has been noted in diabetics^{3,4} and earlier in cases of oxygen want^{5,6} and especially at high altitudes.⁷ This has led to the presentation of the theory,⁸ recently experimentally confirmed by Hasselbalch⁹ that it is the

¹ HALDANE and PRIESTLEY: *Journal of physiology*, 1905, xxxii, p. 225.

² FITZGERALD and HALDANE: *Journal of physiology*, 1905, xxxii, p. 486.

³ BEDDARD, PEMBREY, and SPRIGGS: *Journal of physiology*, 1908, xxxvii, p. xxxix.

⁴ PORGES, LEIMDORFER and MARKOVICI: *Zeitschrift für klinische Medizin*, 1911, lxxiii, p. 389.

⁵ BOYCOTT and HALDANE: *Journal of physiology*, 1908, xxxvii, p. 355.

⁶ HALDANE and POULTON: *Journal of physiology*, 1908, xxxvii, p. 390.

⁷ WARD: *Journal of physiology*, 1908, xxxvii, p. 378.

⁸ WINTERSTEIN: *Archiv für die gesammte Physiologie*, 1911, cxxxviii, p. 167.

⁹ HASSELBALCH: *Biochemische Zeitschrift*, 1912, xlvi, p. 403.

H-ion concentration of the arterial blood which is the main factor in the regulation of breathing. In this paper I shall deal with variations in the alveolar CO_2 tension in man found after the ingestion of food and with the subject in different postures, which are difficult to explain by changes in the quantity of acids in the blood other than H_2CO_3 , and which point to another factor in the regulation of respiration.

METHOD

The Haldane¹ method of determining the alveolar air was used in the cases quoted in this paper. In this method one collects and analyzes a sample of the last part of an expiration, which is alveolar air. To get information as to the average composition of the air in the alveoli, two samples are taken, one at the end of inspiration, when the CO_2 content is naturally lowest, and the other at the end of expiration, when it is highest. The technique of the method requires quite normal breathing for a minute or more; then at the end of a normal inspiration, the subject expires rapidly and fairly deeply through a long tube of about three-quarters inch (19 mm.) diameter; at the end of this expiration the subject seals the tube with his tongue (or a valve is used to close the end through which he breathed); a sample of the air in the tube near the mouthpiece is then taken and later analyzed. Similarly another sample is taken when the rapid deep expiration is made at the end of a normal expiration. The chief criticism of and difficulty in the Haldane method has been that the subject, being conscious of his breathing, is unable to breathe naturally before the taking of a sample; a deeper breath just before the sample is taken leads to a too low result. In experimenting on new subjects for the first time one often notices this tendency to breathe deeply, which when two determinations are made, one a few minutes after the other, generally leads to widely varying results. But with nearly every subject after the first day satisfactory samples are obtained, as practically everybody can learn to breathe naturally, even while conscious of his respiration. As

¹ HALDANE and PRIESTLEY: *loc. cit.*

a check that the breathing has been normal before taking the samples, most of the figures given here are the average of two or more determinations; the duplicates usually agree very closely (within one part in forty). In some of the earlier experiments of this series but one sample of the alveolar air was taken, that after a normal inspiration; the differences found in the alveolar air when one sample was taken were all verified by later experiments where the average of the two samples was taken; in fact the relation between the inspired and expired samples at rest was found to be very constant.

The subjects in these experiments were all young men from twenty to thirty years of age, most of them being medical students and none of them being engaged in heavy muscular work.

To show the variations in the normal alveolar CO₂ tension in subject over a period of several months, the following figures are given for two subjects; all the results are with the subject sitting and in the breakfastless (nüchtern) condition, and each figure represents the average for one day.

H. — 38.5, 38.5, 37.6, 39.9, 37.7, 39.0, 39.5, 40.0, 37.9, 39.4, 38.7, 37.9, 38.9, 39.9, 38.9, 38.4, 37.4, 36.6, Av. 38.6 mm. (Hg) CO₂ tension (i.e., \pm about 2 mm.).

M. — 41.0, 43.5, 43.4, 42.6, 42.4, 42.8, 41.8, 41.7, Av. 42.4 mm. (Hg) CO₂ tension (\pm about 1 mm.).

Thus as noted by Haldane and Priestly, there is a distinct, but different average for each of the two subjects. There are small but distinct differences on different days with the same subject.

To show about how much variation may be expected on the same day with a subject, the following figures are given, which are the alveolar CO₂ tensions on successive hours (9 A.M. to 4 P.M.) when no food was taken.

H. — 39.5, 37.6, 36.9, 38.7, 39.6, 38.9, 38.2, 38.8, Av. 38.5 mm. (Hg) CO₂ tension (\pm 1.6 mm.).

No marked diurnal variations were noticed.

EFFECT OF TAKING FOOD UPON THE ALVEOLAR CO₂ TENSION
WITH THE SUBJECTS IN A SITTING POSITION

Porges, Leimdorfer, and Markovici mention that the CO₂ tension of the blood¹ was raised above the nüchtern value after the subject had taken breakfast. The higher CO₂ tension of the blood after food is ascribed by these authors to the flow of gastric juice in the stomach. The reasoning is that with the withdrawal of HCl from the blood, the latter becomes more alkaline; therefore, a higher tension of CO₂ is required to keep the H-ion concentration of the blood at a point sufficiently high to stimulate the respiratory centre. But in this connection one must remember that although acid is taken from the blood to form gastric juice, alkali is also taken to form pancreatic juice (in amounts more than enough to neutralize the gastric juice). While it is true that the gastric juice begins to flow before the pancreatic juice, it is not very much over 15 minutes under any circumstances, and even less with liquid nourishment. But owing to the earlier flow of the gastric juice and the fact that for a time this loss of acid will be felt only by the blood and not by the body fluids as a whole, one must concede that this may be the cause of the raising of alveolar air. But on the other hand, if the blood became much more alkaline by reason of the flow of gastric juice, one would expect that the urine would become more alkaline immediately after eating; but that this is not invariably the case, has been shown by Hasselbalch.²

Table I gives the results of experiments made where the

¹ *Loc. cit.* Their method, which represents the CO₂ tension of the venous blood rather than that of the arterial blood, gives a value about 20% higher than the alveolar CO₂ tension; but the changes noted in their paper with a resting subject are probably coincident with similar changes in the alveolar CO₂ tension.

² *Loc. cit.* Tables II and III in Hasselbalch's article show almost invariably a higher acidity (H-ion concentration) in the urine for the period (No. 2) immediately after a meal than for the preceding breakfastless period (No. 1). Results (unpublished) by Dr. Smillie of the Harvard Medical School show similar tendencies for the period following food. Determinations in several of the experiments reported here show no marked difference between the breakfastless and food periods.

TABLE I
EFFECT OF FIRST MEAL OF DAY UPON THE ALVEOLAR CO₂ TENSION,
SUBJECT SITTING

| Subject | | | (mm. Hg) | | | | | |
|---------|--------------|----------------|-------------------|-------------------|-------------------|-------|--------|-------------------|
| | Date 1913 | Before food | After food | | | | | |
| | | | $\frac{1}{4}$ hr. | $\frac{1}{2}$ hr. | $\frac{3}{4}$ hr. | 1 hr. | 1½ hr. | 2 hr. |
| Br. | Mar. 17 | 38.8 | — | 45.0 | — | 44.5 | — | 44.1 |
| Bz. | Feb. 5 * | 39.4 | 42.6 | 41.5 | — | 41.8 | 40.2 | — |
| R. | Apr. 11 | 37.0 | — | — | — | — | — | 39.4 |
| U. | 5 | 34.8 | — | — | — | 37.6 | — | — |
| H. | Feb. 8 | 37.6 | 40.0 | 39.3 | 38.5 | 40.3 | 39.7 | 40.6 ¹ |
| | 28 | 36.2 | 38.5 | — | — | 41.0 | 40.6 | — |
| | Mar. 6 | 39.5 | — | — | — | — | — | — |
| | 7 | 37.8 | — | — | — | 41.1 | — | — ² |
| | 8 | 40.0 | — | — | — | 41.4 | — | — |
| | 20 | 39.4 | — | 41.3 | — | — | 42.0 | — ³ |
| | 21 * | 38.7 | — | — | — | 41.6 | — | — |
| | Apr. 3 | 38.9 | — | — | — | — | 42.0 | — |
| | May 1 | 38.4 | — | — | — | 41.3 | — | — |
| | Dec. 20 | 36.6 | — | 40.2 | — | — | 40.7 | — |
| M. | Feb. 10 | 41.1 | 42.6 | 42.6 | — | 43.0 | 44.2 | 44.0 ⁴ |
| | 19 * | 43.5 | — | 45.0 | — | 45.6 | 45.9 | — |
| | Mar. 6 * | 42.8 | — | 44.5 | — | 44.4 | — | 44.4 ⁵ |
| | 19 | 41.8 | — | 43.4 | — | 42.6 | — | 43.3 ⁶ |

¹ $\frac{1}{2}$ hr. 39.8² $\frac{3}{4}$ hr. 39.9.³ A second meal was taken 2 hr. after the first and the alveolar CO₂ continued 1 hr. 40.3; 2 hr. 41.2.⁴ $\frac{1}{2}$ hr. 45.2. A second meal was taken 3 hr. after the first and the alveolar CO₂ continued $\frac{1}{2}$ hr. 44.4; 1 hr. 43.8; 2 hr. 43.3; 3 hr. 44.4.⁵ $\frac{3}{4}$ hr. 45.8; 4 hr. 44.1; 5 hr. 43.9; 6 hr. 43.3.⁶ $\frac{3}{4}$ hr. 42.8; 4 hr. 44.1.

NOTE. — On days starred, coffee was taken.

alveolar air was taken before and at varying intervals after the taking of food. The rise of the alveolar CO_2 tension after food is very evident in practically every case. In Table II a similar rise is noted after a non-carbohydrate meal in the case of normal individuals where an acidosis had been produced. The presence of carbohydrate in the diet is thus obviously not essential to this rise, although generally considered as the important factor in reducing an acidosis. The rise is still manifest after one and one-half hours in every case but one.¹

The effect of a second meal on the alveolar air, while the effect of the first meal was still evident, is shown in two cases; no further rise is evident, showing the effect of food is not cumulative.

TABLE II

EFFECT OF THE FIRST MEAL OF THE DAY UPON THE ALVEOLAR CO_2 TENSION,
WHERE THE MEAL CONTAINS NO CARBOHYDRATES

| Subject and date (1912) | (mm. Hg) | | | | | | | | |
|--|----------|------|------|---------|---------|---------|------|---------|------|
| | H | | | Ha. | K. | S. | | C. | |
| | Nov. 6 | 7 | 8 | Dec. 22 | Dec. 28 | Dec. 29 | 30 | Dec. 29 | 30 |
| Before food | 35.8 | 31.0 | 30.1 | 39.2 | 28.4 | 37.6 | 37.1 | 39.9 | 38.4 |
| After food ¹ | 38.8 | 33.4 | 31.9 | 39.1 | 30.3 | 40.3 | 40.9 | 40.7 | 40.6 |
| No. of days immediately preceding on which sub- ject has had no carbohy- drate | 0 | 1 | 2 | 0 | 1 | 1 | 2 | 1 | 2 |

¹ 1-1½ hr.

Sugar. When 100 g. of cane sugar was taken, the rise in the alveolar CO_2 tension was again found, but it lasted for a little less than an hour.

¹ Compare HASSELBALCH: *loc. cit.*

TABLE III
EFFECT ON THE ALVEOLAR CO₂ TENSION OF TAKING 100 GRAMS OF
CANE SUGAR SOLUTION

| Subject | Date (1913) | (mm. Hg) | | | | | |
|---------|-------------|---------------------|--------------------|-------------------|-------|--------------------|-------------------|
| | | Before taking sugar | After taking sugar | | | | |
| | | | $\frac{1}{4}$ hr. | $\frac{1}{2}$ hr. | 1 hr. | $1\frac{1}{2}$ hr. | 2 hr. |
| H. | Feb. 18 | 37.4 | 39.0 | 39.2 | 37.8 | 37.8 | 36.6 |
| | Mar. 18 | 37.9 | 39.9 | 38.6 | 37.8 | 37.7 | 38.9 ¹ |

¹ At the close of this experiment food was taken, and the alveolar CO₂ tension rose to 41.3 mm.

Beefsteak. The effect of eating a small beefsteak was tried. The cooking was done in the room with the subject, and alveolar air determined during that period. But no rise in the alveolar CO₂ tension was noticed which might be ascribed to psychic flow of the gastric juice, although after eating, the CO₂ tension rose as usual.

EFFECT OF 80 GRAMS OF BEEFSTEAK ON THE ALVEOLAR CO₂ TENSION

Before 37.4 mm. During cooking 37.6 mm. After eating ($\frac{1}{2}$ hr.) 38.8 mm.; ($1\frac{1}{2}$ hours) 40.1 mm.; (2 hours) 39.0 mm.

Agar-agar. Agar-agar offers the opportunity of producing digestive movements without absorption, with perhaps also some flow of digestive juices. The alveolar CO₂ tension may have become a little higher, but by no means so markedly as with absorbable food.

Summarizing in brief the experiments thus far presented, one may say that there is a rise in the alveolar CO₂ tension after taking food of any sort lasting in general as long as there is active absorption (for example $\frac{3}{4}$ hr. with sugar and 4-6 hr. with less quickly absorbed food). While the rise is probably proportional to the bulk of absorbable food taken, if the total amount is small, yet it does not rise above a certain maximum. The rise is not due to the existence of an acidosis in the breakfastless state, as

TABLE IV

EFFECT ON THE ALVEOLAR CO₂ TENSION OF TAKING 10 GRAMS AGAR-AGAR

| Subject | Date (1913) | (mm. Hg) | | | | |
|---------|-------------|---------------|-------------------|-------|--------------------|-------------------|
| | | Before taking | After | | | |
| | | | $\frac{1}{2}$ hr. | 1 hr. | $1\frac{1}{2}$ hr. | 2 hr. |
| H. | Feb. 8 | 39.0 | 39.0 | 40.3 | 39.8 | — |
| | 15 | 38.5 | 39.1 | 37.6 | 38.6 | 39.8 ¹ |
| M. | 12 | 43.5 | 44.1 | 43.6 | — | 43.0 |

¹ 2 $\frac{1}{2}$ hr. 39.2; 3 hr. 38.3. Food taken 3 $\frac{1}{2}$ hr. after the agar-agar raised the CO₂ tension to 41.6 mm.

immediately after the absorption of food ceases, the breakfastless value is again obtained.

EFFECT OF POSTURE ON THE ALVEOLAR CO₂ TENSION

Experiments, where the alveolar carbon dioxide tension of the same subject was determined in different positions, are summarized in Table V. The postures chosen were standing, sitting, lying on the side, on the back, and in the Trendelenburg position.¹ A comparison was also made of the alveolar carbon dioxide tension of a subject sitting in a reclining and in an erect position.

The experiments seem to show clearly that the alveolar CO₂ tension is lowest when the subject is standing, higher when sitting, and still higher when lying. One can find no decisive difference between the values obtained lying on the back and on the side; but in the Trendelenburg position, the alveolar CO₂ tension is decidedly lower than in the other lying positions and approximates that of sitting. Sitting erect leads to a lower alveolar CO₂ tension than sitting in a reclining position.

The general conclusion to be drawn is that the more relaxed the position, the higher the alveolar CO₂ tension. In one case,

¹ I am indebted to Prof. Y. HENDERSON for suggesting that this position be included.

TABLE V

ALVEOLAR CO₂ TENSIONS IN DIFFERENT POSITIONS (BREAKFASTLESS)

| Subject | Date (1913) | (mm. Hg.) | | | | | |
|---------|----------------|-------------------|-------------------|-----------------------------|------------------|---------------------|--------------------|
| | | Standing | Sitting | Lying Tren- delenburg | Lying on back | Lying right side | Lying left side |
| F. | Dec. 18 | 37.4 | — | — | 40.6 | — | — |
| " | 19 | 37.2 | — | — | 38.3 | — | — |
| Br. | Mar. 17 | 37.3 ² | 38.8 | — | 41.8 | — | — |
| R. | Apr. 11 | 37.2 | 37.0 | — | 40.1 | 42.5 | — |
| U. | 5 | 36.5 | 34.8 | 36.6 | 35.7 | — | — |
| H. | Feb. 18 | — | 37.6 ¹ | — | 39.5 | — | — |
| | 26 | 36.8 | 39.9 | — | 41.6 | — | — |
| | 28 | 34.4 | 36.2 | — | 39.7 | — | — |
| | Mar. 6 | 36.5 | 39.5 | — | — | — | — |
| | 8 | 36.6 | 40.0 | — | — | — | — |
| | 31 | — | 39.4 | 38.8 | 40.8 | — | 40.8 |
| | Apr. 3 | — | 38.9 | 40.2 | 41.3 | 42.2 | 42.3 |
| | May 1 | 35.2 | 38.4 | 40.2 | 40.5 | 41.0 | — |
| | Dec. 13 | 33.5 | — | — | 39.9 | — | — |
| Average | | 35.5 | 38.8 | 39.7 | 40.6 | 41.6 | 41.6 |
| M. | Feb. 19 | 39.1 | 42.8 ² | — | 43.8 | — | — |
| | 21 | 38.8 | 42.8 | — | 44.3 | — | — |
| | Mar. 19 | 40.3 | 41.8 | — | 42.6 | — | — |
| | Apr. 2 | 40.7 | 41.7 | 41.9 | 42.8 | 42.0 | 42.2 |
| Average | | 39.7 | 42.3 | 41.9 | 43.4 | 42.0 | 42.2 |

¹ Sitting erect 37.0; sitting reclining 38.2.² Sitting erect 41.8; sitting reclining 43.8.

U., these differences were not noticed, but with the other subjects the results seem consistently to point to this general conclusion. The order in which the different positions were taken made no difference in the result; the alveolar CO_2 tension for any of the positions assumed its level for the position almost immediately on taking it; alveolar CO_2 tensions determined after three to five minutes were essentially the same as those determined after the subject had been in the position for a longer time. That the changes in the alveolar air due to different postures are not the result of nervous impulses carried from the diaphragm to the respiratory centre, seems to be indicated by the failure to find the highest value in the Trendelenburg position, where there is the largest pressure on the diaphragm.

The results of the experiments on the alveolar CO_2 tension in other positions than sitting when food was taken are given in Table VI. One finds the rise in the CO_2 tension standing after taking food to be fully as large as when the subject is sitting. However, when the subject is lying, the rise is not so large on the average; although in some of the cases it is fully as large as sitting, yet in others there is little or no rise at all.

EFFECT OF OTHER FACTORS ON THE ALVEOLAR CO_2 TENSION

Coffee. Experiments were made on the alveolar CO_2 tension as the result of taking coffee. About 350 c.c. of black coffee were taken in each experiment.

TABLE VII
EFFECT OF COFFEE ON THE ALVEOLAR CO_2 TENSION

| Subject | Date | Before taking | After taking | | | | |
|---------|---------|---------------|-------------------|-------------------|-------|-------|--------------------|
| | | | $\frac{1}{4}$ hr. | $\frac{3}{4}$ hr. | 1 hr. | 2 hr. | $3\frac{1}{2}$ hr. |
| H. | Mar. 21 | 38.7 | 39.3 | — | 37.3 | 36.0 | 38.7 |
| | Oct. 23 | 37.4 | 36.8 | 35.6 | 34.8 | 36.0 | 38.3 |

A fall in the CO_2 tension is noticed in both experiments; but the lowering effect of coffee, as shown in these experiments, was not great enough to overcome the rise in the alveolar CO_2 tension due to the taking of food in previously cited experiments in Table II.

TABLE VI

EFFECT OF FOOD ON THE ALVEOLAR CO₂ TENSION WITH THE SUBJECT IN OTHER POSITIONS THAN SITTING

| Subject | Date (1913) | Standing | | | | Lying on back | | | |
|---------|----------------|----------------|----------------------|---------|---------|-------------------|----------------------|---------|-------------------|
| | | Before food | After food | | | Before food | After food | | |
| | | | $\frac{1}{4}$ -1 hr. | 1-2 hr. | 2-3 hr. | | $\frac{1}{4}$ -1 hr. | 1-2 hr. | 2-3 hr. |
| Br. | Mar. 17 | 37.3 | 40.2 | 40.1 | 40.6 | 41.8 | 42.7 | 43.8 | 43.1 |
| R. | Apr. 11 | 37.2 | — | 39.5 | — | 40.1 | — | 42.5 | — |
| H. | Feb. 28 | — | — | — | — | 39.7 | 41.6 | 40.7 | 40.9 |
| | Mar. 6 | 36.5 | — | 37.5 | 38.5 | — | — | — | — |
| | 8 | 36.6 | 39.1 | 37.4 | — | — | — | — | — |
| | Apr. 3 | — | — | — | — | 41.3 ¹ | — | — | 42.6 ² |
| | May 1 | 35.2 | — | 39.3 | — | 40.5 ³ | — | 43.3 | — ⁴ |
| M. | Feb. 19 | — | — | — | — | 43.8 | — | 43.3 | — |
| | Mar. 1 | — | — | — | — | 41.8 | 42.4 | 40.7 | 43.0 |
| | 19 | 40.3 | 41.3 | 40.5 | 40.7 | 42.6 | 44.5 | 46.3 | 45.8 |
| F. | Dec. 18 | 37.2 | 39.9 | 41.2 | — | 40.6 | 42.3 | 43.9 | — |
| | 19 | 37.4 | — | 40.4 | — | 38.3 | 41.9 | 41.7 | — |

¹ Lying right side 42.2; left side 42.3; Trendelenburg 40.2.

² Lying right side 43.9; left side 44.5; Trendelenburg 42.9.

³ Lying right side 41.0; Trendelenburg 40.2.

⁴ Lying right side 42.8; Trendelenburg 41.9.

Aromatic Spirits of Ammonia.—The effect on the alveolar CO₂ tension of smelling aromatic spirits of ammonia for a half minute was tried. In the case of K., who a few moments previously had recovered consciousness after fainting, the smelling of the aromatic spirits of ammonia caused the alveolar CO₂ tension to drop from 42.4 to 38.9 mm.; this drop was coincident with the return of color to the face. In the case of H. (who was not faint) the drop was not so great, being from 39.6 to 38.6 mm.

DISCUSSION

While it is perhaps not yet possible to lay down any hard and fast rule as explaining the results obtained, there are many coincidences in connection with these experiments that it is well to note. It seems highly probable that the rise in the alveolar air following the intake of food and that following the taking of a more relaxed position have much in common. It is well known that drowsiness is very often noticed after a heavy meal and also that it is more prone to appear in a reclined or relaxed position. Thus, one may conclude that drowsiness is more likely to be evident with a high alveolar CO_2 tension. One finds vasodilation in the skin or splanchnics, the former in a relaxed position and the latter after food; thus it will appear that the higher alveolar air is also coincident with vaso-dilation; where there is vaso-dilation from both food and position, as after food when in a lying position, there is not noticed in some cases marked cumulative effect to raise the alveolar CO_2 tension by reason of both factors. The fact that the rise in the alveolar CO_2 tension lasts only so long as there is active digestion and absorption of food, and the fact that coffee, a vasoconstrictor, lowers the alveolar CO_2 tension, furnish additional evidence to point to the fact that vasodilation and a high alveolar CO_2 tension and vasoconstriction and a low alveolar CO_2 tension run parallel. The anatomical position of the two centres — the respiratory and the vasomotor — confirm the possibility that the same impulse might affect both at the same time.

Hasselbalch¹ reports that the H-ion concentration* of the blood, other things being equal, increases with the concentration of the blood corpuscles; unless there is a diminution of the blood corpuscles in the blood entering the respiratory centre in a relaxed position or after food, it seems that some other factor beside the H-ion concentration must be exerting an influence upon the respiratory centre.

¹ *Loc. cit.*

CONCLUSIONS

1. The alveolar CO_2 tension rises after the intake of food and remains high so long as the food is in active digestion.
2. The alveolar CO_2 tension is higher when one is in a relaxed position than when one is in an erect position. Thus the alveolar CO_2 tension is markedly higher standing than sitting, and higher sitting than lying.
3. The taking of coffee, without food, caused a fall in the alveolar CO_2 tension.
4. These variations, especially those from changing position, do not appear to be due to changes in the H-ion concentration of the blood (independent of the H_2CO_3); but apparently some other agent is affecting the respiratory centre to cause these changes.
5. A high alveolar air is coincident with vasodilation, and a low alveolar CO_2 tension with vasoconstriction.

